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A CASE OF ALLERGY TO COMMON FOODS*

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The idiosyncrasy of certain individuals to common foods has been recognized for many years, but until recently our knowledge has depended mainly on isolated clinical observations, and the essential causes of the condition have remained obscure.

Through the courtesy of Dr. Eli Long of this city I have had the opportunity to investigate a case of pronounced idiosyncrasy to eggs, almonds and oats in a child 8 years old, the data from which furnish the basis of this communication. At the very outset I wish to acknowledge my great indebtedness to Dr. Long for the privilege of observing the case and for a number of valuable suggestions.

I. HISTORY

Family History.—The maternal grandmother is affected with ichthyosis; with this exception the family history is irrelevant.

Personal History.—The patient, an only child, was born at term, May 10, 1904. Delivery was by low forceps and the infant was entirely normal. He was breast-fed for eighteen months and received no supplementary food until over a year old. The first teeth erupted when the patient was ten months old; he walked at the age of 18 months.

Previous Illness.—Beginning at the age of 3 months the patient was affected with seborrheic eczema of the face, head and limbs, which showed periods of improvement and recrudescence during the first year. At the age of 9 months he had a very severe attack of coryza. During the first 3 years of life the patient had a number of general convulsions, the first of which appeared at the age of 18 months. During this period there was evidence of a mild grade of rickets.

The patient has been subject to rather frequent attacks of inflammation of the respiratory tract. At the onset the symptoms resembled hay fever—frequent sneezing, lachrymation and coryza with a clear mucoid discharge. Attacks resembling bronchial asthma have been frequent, usually during the course of an infectious cold.

For a number of years the child has had a chronic scaly skin eruption which is most pronounced on the hands and arms but which has at various times affected the entire body. This rash is usually associated with itching. The severity and extent of involvement varies greatly from time to time. At times the rash has improved greatly and has almost disappeared, usually when he was on a restricted diet.

The patient has been free from all of the common infectious diseases.

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Idiosyncrasy to Egg.—The child was first given egg when 10 days old, at which time he was suffering from a slight attack of diarrhea. The white of an egg was administered in barley water and caused no symptoms whatever. The next time egg was given the patient was 14 months old, when he showed the characteristic symptoms of egg intolerance. The attempt was made to feed a soft boiled egg, of which the child took only a few tastes, cried, and refused more. Almost immediately he began to claw at his mouth and the tongue and buccal tissues swelled until they reached a size many times greater than normal. Around the mouth a distinct crop of urticarial wheals appeared. Subsequent to this experience the child refused to eat soft boiled egg.

Toward the end of his second year the action of egg on the skin was noted. The child would frequently play with empty egg shells, which always gave rise to an urticarial rash over the hands and arms.

When 22 months old egg was administered the third time. About one-eighth of an egg-white was given in milk. The child vomited immediately, the lips, tongue and inner surfaces of the cheeks became swollen and a general urticarial rash appeared.

When 2 years old, in order to determine the exact effect of egg, he was given a small quantity of partially coagulated egg-white between slices of bread. Only a very small amount was swallowed and almost immediately he began to gag and vomited profusely. The child became extremely ill. The lips, tongue and buccal tissues became enormously swollen and urticarial wheals appeared around the mouth. His face was flushed, the respirations were rapid and the mental condition dull. He soon fell into a restless sleep from which he awoke in a few moments and vomited several times. He went to sleep again and awoke after two and a half to three hours apparently well.

The next experience with egg occurred eight months later when the child ate a few small cakes in the preparation of which egg was used. Within a few moments he began to vomit and the characteristic swelling of the lips and tongue appeared. The swelling subsided within an hour.

From this time the patient was carefully guarded from all food which might contain egg, but in April, 1910, he ate a small portion of a roll the top of which was glazed with egg. The lips and tongue swelled and hives appeared around the mouth.

Idiosyncrasy to Almonds.—Two years ago the patient was given an almond for the first time. Very soon he complained of a queer feeling in his throat and within a few moments the characteristic swelling of the tongue, lips and mouth appeared. Other nuts had been eaten at various times with no ill effect.

Idiosyncrasy to Oatmeal.—During an attack of gastro-enteritis at the age of 22 months the patient was given a single feeding of oatmeal jelly from which no symptoms were observed. Oatmeal caused symptoms similar to but much milder than those due to eggs or almonds. Usually urticarial wheals appeared around the mouth and on one occasion vomiting occurred.

Examination.—Physical examination disclosed nothing of importance beyond the skin rash noted in the personal history. The skin of the hands and arms, and, to a lesser degree, of the trunk and lower extremities was dry and covered with fine scales. The individual scales were quite small and at most times the condition amounted to nothing more than a roughening of the skin. When the rash was at its maximum it was accompanied by itching.

The blood was examined twice with the following result: May, 1911: Hemoglobin 70 per cent. (Sahli), red cells 4,800,000, white cells 10,000. The differential count of 1,000 cells showed, polynuclear nutrophil cells, 70 per cent.; mononuclear cells, 18.6 per cent.; eosinophil cells, 10.1 per cent.; mast cells, 0.7 per cent. Oct. 7, 1911, the differential count was as follows: Polynuclear neutrophil cells, 68.1 per cent.; mononuclear cells, 19.2 per cent.; eosinophil cells, 11 per cent.; mast cells, 1 per cent. An examination of the urine at this time disclosed nothing abnormal.

DISCUSSION

The main problems for investigation in this case are indicated by the history. The patient exhibited an idiosyncrasy toward eggs, almonds and oatmeal, foods which are entirely harmless to the normal individual. It seemed of importance to ascertain, if possible, the constituents of the foods which were responsible for the toxic symptoms. The underlying cause of the patient's allergic condition, and a means to overcome it, seemed also problems for investigation.

II. THE REACTION

At the very outset it was necessary to devise some test other than actual feeding by which the toxic substances could be identified. Owing to the decided and at times alarming symptoms produced by the ingestion of the toxic foods, this method of investigation was considered unjustifiable.

Cutaneous inoculations on the basis of the von Pirquet tuberculin test were tried. The "borer" devised by v. Pirquet was used to produce a uniform abrasion of the skin, into which the substance to be tested was gently rubbed. The active substances produced a distinct urticarial wheal at the site of inoculation, which appeared within five to fifteen minutes after the test was made.[1] The intensity of the reaction varied but with the more active substances a wheal 1.5 to 3 cm. in diameter, which was elevated 1 to 5 mm. above the surrounding skin, was often produced. In stronger dilutions the active substances caused typical urticarial wheals by mere contact with the unbroken skin. The reaction was always immediate and always disappeared within one-half to one hour. After this time the skin abrasion only marked the site of inoculation.[2]

1. In a case of buckwheat poisoning observed by Smith (Arch. Int. Med., 1909, iii, 350), a cutaneous inoculation of this substance caused a large urticarial wheal to appear at the abraded surface. A general reaction also occurred.

2. Schmidt (Beiträge zum Studium der cutanen Allergien, Arch. f. Kinderh., 1910, liii, 349) has made cutaneous tests with food substances on children of different ages. He used for this purpose "puro," which consists of egg white and beef extract, and a milk preparation. The positive reaction as described by him was an area of redness or a raised papule which appeared eight to twenty-four hours after the inoculation and was analogous to the reaction to tuberculin. The positive reactions bore no relation to the disease with which the children were affected but Schmidt observed that the percentage of reactions increased with age. So far as I am aware these observations have not been confirmed and out of a great number of cutaneous tests with food substances I have never observed a clearly positive reaction of this variety. In some instances the site of inoculation would show a slight redness after twelve to twenty-four hours which at times was a trifle greater perhaps than the control. But in no instance was the redness sufficiently marked to be conclusive and the formation of a distinct papule was never observed.

Itching was a frequent accompaniment but was not constant. Usually it was present with the more pronounced reactions, and always when urticarial wheals were produced by the contact of active substances with the unbroken skin.

In order that this reaction could be used as the basis of experimental work it was necessary to show that it was specific and to determine whether it could be produced by chemical or mechanical irritation alone. Pursuant of this, numerous control experiments were made.

The mechanical irritation produced by the borer alone, or by inoculation of inert substances into the abrasion, always caused a slight swelling at the abraded surface. This traumatic reaction was slightly greater, perhaps, than that present in normal persons, but was never sufficiently marked to cause any confusion. The abrasion gave rise to a perfectly circular papule about 1 to 2 mm. in diameter and identical with the slight reaction which sometimes appears immediately after a v. Pirquet tuberculin test.

On a number of occasions tests were made to ascertain if the patient was subject to factitious urticaria, but always with negative results. Inoculation of acids in different strengths (acetic, formic, picric, sulphuric, nitric, hydrochloric, oxalic and citric) gave no evidence of the true reaction. Alkaline substances in varying dilution (carbonates and hydroxids of sodium, potassium and ammonium) were also inactive. Numerous tests were made with solutions of salts (copper sulphate, ammonium chlorid and sulphate, sodium chlorid and citrate, uranium acetate, ferrous sulphate, etc.), all of which gave negative results. Tests were also made to determine whether the various reagents used in the preparation or extraction of the different substances to be tested might cause or inhibit the reaction. In no instance could such action be demonstrated.

These experiments showed that the cutaneous reaction was not the result of chemical or mechanical irritation. Other experiments to be described later showed that the cutaneous reaction was caused only by certain food substances and to a marked degree only by those to which the patient had exhibited a pronounced idiosyncrasy.[3]

The occurrence of an urticarial lesion from cutaneous inoculation of the toxic foods was directly comparable to the more striking effects produced by their ingestion — urticaria and swelling of the tissues with which they had come in contact. The swelling was strictly analogous to angioneurotic edema which is closely related to urticaria if not identical with it. The symptoms due to ingestion occurred immediately, the cuta-

3. Control tests with preparations of eggs, almonds and oats to which the patient showed a marked reaction, were made on twenty children—from two to eight years of age—and on four adults. In no case was a reaction produced.

neous reaction was also immediate. The cutaneous reaction was considered therefore as direct evidence of the toxic nature of the substance tested.

III. EXPERIMENTS WITH HEN'S EGGS

A. Egg-White

General.—Egg-white liquefied by cutting and diluted with distilled water produced a cutaneous reaction in the dilutions shown in Table 1.[4]

TABLE 1.—EGG-WHITE DILUTED WITH DISTILLED WATER

Dilution	Reaction*	Dilution	Reaction
1 to 200	—	1 to 50	+
1 to 150	±	1 to 20	+u
1 to 100	+	1 to 10	+u
1 to 75	+		

* + and — indicate positive and negative reactions, respectively; ± indicates a reaction which was suggestive or at one time positive and at another negative; u indicates urticaria by contact with the unbroken skin. These symbols will be used throughout the paper.

Experiments were then undertaken to determine the nature and properties of the toxic substance (or substances) in egg-white.

1. Dialysis of egg-white through a collodion membrane against distilled water for varying periods up to seventy-two hours showed that the active substance was not diffusable. The dialysates when tested plain or after concentration to a small volume were incapable of causing a cutaneous reaction.

2. Alcohol (95 per cent.) and ether extracts and the residues obtained by complete evaporation of the solvents were inert. The residues insoluble in alcohol and ether were capable of causing a marked reaction.

3. The active substances were completely precipitated by saturation with ammonium sulphate. The filtrates freed from ammonium sulphate by dialysis, or by heating with barium carbonate, were inert. The precipitate was extremely active.

4. Egg-white was coagulated by heat and acetic acid. The filtrate was concentrated to a small volume and freed from protein by precipitation with alcohol. The protein-free filtrate was inert.

These experiments indicated that the toxic action of egg-white was due to the protein substances or to some substance intimately connected with them.

Experiments with Proteins Isolated from Egg-White.—Despite the vast amount of study devoted to the separation and properties of the

4. Throughout the experimental work a control test was made with each series of experiments, using distilled water or some substance previously found to be inert. All of the experiments were made at least twice; a number were repeated many times.

proteins of egg-white, the exact relationship and nature of some of the substances isolated by different workers is not clearly established.[5]

It is not my intention, nor is it within the province of this paper to discuss the unity or the chemical relationship of the various proteins separated from egg-white. The attempt has been made to isolate protein substances which are apparently distinct in order to ascertain if possible the protein fraction — or fractions — responsible for the patient's symptoms.

Five proteins were separated — ovomucin, ovoglobulin, ovalbumin, ovomucoid and conalbumin. These terms refer only to the substances isolated by the methods followed. Ovalbumin was obtained in crystalline form by the method of Hopkins[6] and was purified by recrystallizing three times. Ovomucin was prepared by diluting egg-white with four volumes of distilled water, dissolving the precipitate in a weak solution of sodium hydroxid and reprecipitating with dilute acetic acid. This procedure was repeated four to five times, the precipitate being thoroughly washed between each precipitation.

The fractions called ovoglobulin were obtained as follows: Egg-white was precipitated by half saturation with ammonium sulphate, the precipitate mixed with a small amount of distilled water and dialysed against running water for twenty-four hours. A rather heavy precipitate in mucin-like threads and flakes settled out. This precipitate was thoroughly washed with water, pressed between layers of filter paper and dried in a current of air from an electric fan. This fraction was called Ovoglobulin 1.

To the filtrate was added three-eighths volume of a saturated solution of ammonium sulphate, the resulting precipitate mixed with water and

5. Two protein fractions can be separated with a considerable degree of sharpness, ovalbumin and ovomucoid. The former can be obtained in crystalline form. The latter, owing to the fact that it is not coagulated by heat and is precipitated by alcohol without losing its solubility in water, can be obtained free from coagulable protein. There is some uncertainty concerning the relationship of ovoglobulin and ovomucin. The ovomucin of Eicholtz (The Hydrolysis of the Albumins, Jour. Physiol., 1898, xxiii, 163) was obtained by diluting egg white with water and is considered by some to belong to the globulin fraction. Osborne and Campbell (The Protein Constituents of Egg-White, Jour. Am. Chem. Soc., 1900, xxii, 423) used the term ovomucin for a considerable portion of the fraction precipitated from egg-white by one-half saturation with ammonium sulphate. They considered that their ovomucin was identical with that of Eicholtz. Langstein (Ueber die gerinnbaren Stoffe des Eierklars, Beitr. z. chem. Phys. u. Path., 1902, i, 83) objects to the term ovomucin and with Corin and Berard (Beitrag zum Studien der Albumenstoffe Eierweiss. Jahresb. d. Fortschr. d. Tier-Chem., 1888, xviii, 13) believes that there is more than one globulin in egg-white. A non-crystalline albumin with a lower coagulation temperature than the crystalline form has been described by Osborne and Campbell, and later by Langstein. This substance has been termed conalbumin.

6. Hopkins: On the Separation of a Pure Albumin from Egg-White, Jour. Physiol., 1900, xxv, 307.

filtered. A considerable portion of the precipitate remained on the filter. The insoluble residue was washed with water and dried in the same manner as Ovoglobulin 1. This fraction was called Ovoglobulin 2.

The opalescent filtrate was dialysed against running water for twenty-four hours. No precipitation occurred. The solution was precipitated by one-third saturation with ammonium sulphate, the precipitate redissolved in water and again dialysed. This dialysed solution was used for the cutaneous test as Ovoglobulin 3.

Ovomucoid was prepared by the method of Mörner.[7] Liquefied egg-white was poured into boiling water acidulated with acetic acid. The mixture was heated in the presence of a sufficient quantity of acetic acid to precipitate all of the coagulable protein. The filtrate was concentrated on the water-bath and the ovomucoid precipitated by pouring into four volumes of alcohol. Purification was effected by redissolving in water and reprecipitating by alcohol several times, solution in water, dialysis for twenty-four hours, and final precipitation by alcohol.[8]

TABLE 2.—TESTS WITH PROTEINS ISOLATED FROM EGG-WHITE

Solution	1-20,000	1-15,000	1-10,000	1-5,000	1-1,000	1-500	1-100	1-10
Ovomucin dissolved in 0.5 per cent. sod. carb.	—	—	—	+	+	+	+u	+u
Ovoglobulin 1 dissolved in 0.5 per cent. sodium carbonate solution	—	—	—	+	+	+	+u	+u
Ovoglobulin 2 in 0.5 sodium carbonate solution	—	—	—	±	+	+	+u	+u
Ovoglobulin 3	—	—	—	—	—	—	—	—
Ovalbumin, dissolved in distilled water	—	—	—	—	—	—	±	+
Ovomucoid dissolved in distilled water	±	+	+	+u	+u	+u	+u	+u
Conalbumin dissolved in 1 per cent. sodium carbonate solution	—	—	—	—	—	—	—	—
Conalbumin liquefied by artificial gastric juice	—	—	—	—	—	—	—	—

Conalbumin was prepared by the method of Langstein (see note 5). These protein fractions were used for the skin test with the results shown in Table 2.

These tests show that ovomucoid was the most active protein and was capable of causing a cutaneous reaction constantly in dilutions of 1 to 15,000 and frequently in dilutions as high as 1 to 20,000. Ovomucin and the fractions called Ovoglobulin 1 and 2 were next in activity. According to our present knowledge these three fractions are identical

7. Mörner: Ueber ein im Hühnereiweiss in reichlicher Menge vorkommende Muzinsubstanz, Ztschr. f. physiol. Chemie, 1894, xviii, 525.

8. I am indebted to Dr. Eddy (On the Synthesis of Some Protein Salts, Dissert. Columbia Univer., 1909) for a considerable quantity of very pure ovomucoid which he had carefully prepared for use in previous experiments.

(Osborne and Campbell, Eicholtz). Conalbumin and the fraction called Ovoglobulin 3 were incapable of causing a reaction. Ovalbumin was active only in a comparatively concentrated solution. In consideration of the fact that the first separation of ovalbumin takes place in a liquor rich in ovomucoid, and owing to the activity of ovomucoid in high dilution, it was considered possible that the reaction produced by ovalbumin was dependent on a small amount of ovomucoid mechanically incorporated in or adherent to the crystals. That such was true is indicated by the following experiment:

A concentrated solution of ovalbumin was coagulated by heat and acetic acid. The coagulum, thoroughly washed with distilled water and liquefied by the action of artificial gastric juice or dissolved in 1 per cent. sodium hydroxid solution, caused no reaction.[9]

The toxic action of egg-white was due, therefore, to the protein ovomucoid and to the fractions called ovomucin by Osborne and Campbell and Eicholtz.

B. Experiments with Egg-Yolk [10]

Egg-yolk was capable of producing a cutaneous reaction in the dilutions shown in Table 3.

TABLE 3.—EFFECT EGG-YOLK DILUTED WITH DISTILLED WATER

Dilution	Reaction	Dilution	Reaction
1 to 50	—	1 to 10	+
1 to 20	—	1 to 5	+
1 to 15	±		

The activity of egg-yolk was shown to be about one-tenth as great as egg-white.

Experiments demonstrated that the active constituents of egg-yolk were completely precipitated by saturation with ammonium sulphate, were insoluble in alcohol or ether and were not diffusible through collodion membranes. These properties would seem to indicate that the toxic substances belonged to the protein constituents.

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9. Control experiments with the active proteins showed that the action of gastric juice for several hours or even days, was incapable of preventing the reaction. The same was true of the action of sodium hydroxid.

10. To obtain the yolks entirely free from egg-white the following procedure was used: The yolks were first washed as free as possible from the white by the method of Pennington (A Chemical and Bacteriological Study of Fresh Eggs, Jour. Biol. Chem., 1909, vii, 109) and then treated with 95 per cent. alcohol which served to harden the vitelline membrane and to coagulate any trace of white adherent. The alcohol was poured off and the remaining traces removed by gently blotting with filter paper. A fine pointed pipette was passed through the vitelline membrane into the center of the yolk mass. The fluid yolk was aspirated into the pipette and blown into suitable receptacles, the first and last portions in the pipette being discarded as a further precaution.

Ovovitelline was prepared by the method of Weyl,[11] dissolved in 0.5 per cent. solution of sodium carbonate, and tested on the patient. No reaction occurred.

IV. EXPERIMENTS WITH ALMONDS

General.—An emulsion of ground almonds produced a marked cutaneous reaction and the following experiments were undertaken to determine the nature of the toxic constituents:[12]

1. A substance capable of causing the reaction was diffusible through both collodion and parchment membranes. This activity of the dialysate was dependent on a protein substance which gave positive tests for proteose. About 10 gm. of finely ground almonds were dialysed through collodion against 100 c.c. of distilled water. The separate dialysates for each twenty-four hours were concentrated to a small bulk on the water-bath and used for the skin test. The results are shown in Table 4.

TABLE 4.—DIALYSIS OF AN EMULSION OF ALMONDS THROUGH COLLODION

Period of Dialysis	Cutaneous Reaction	Biuret Reaction
First 24 hours	+	+
Second 24 hours	+	+
Third 24 hours	+	+
Fourth 24 hours	+	+
Fifth 24 hours	+	+†
Sixth 24 hours	*	—
Seventh 24 hours	—	—

*Suggestive. †Very faint.

At the conclusion of the experiment the contents of the bag gave a positive cutaneous reaction and a strong biuret test.

2. Aqueous and 10 per cent. saline extracts of almonds were freed from protein by treatment with heat and acetic acid, concentration of the filtrate and complete precipitation of the remaining protein by alcohol. The precipitate in each instance was quite active, the protein-free filtrate was inert.

3. Saturation of an aqueous or a 10 per cent. saline extract of almonds with ammonium sulphate precipitated all of the active constituents. The filtrate when tested plain, or when freed from ammonium sulphate, was entirely inert.

4. The active substances were not soluble in alcohol (95 per cent.) or ether.

These experiments indicated that the active constituents of almonds belong to or were intimately connected with the proteins.

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11. Weyl: Abderhalden's Handb. d. Biochem. Arbeitsmeth., 1910, ii, 381.

12. The almonds used in the experiments were freed from the brownish outer skins by drenching for a few moments with boiling water, since it had been found by previous experiment that these skins were incapable of causing a cutaneous reaction.

Experiments with Proteins Isolated from Almonds.—The globulin amandin[13] was extracted by treating finely ground almonds with 10 per cent. sodium chlorid solution for twenty-four hours. The extract was saturated with ammonium sulphate. The precipitate, dissolved in 10 per cent. sodium chlorid solution, was dialysed through collodion. The amandin was precipitated as a viscid, semiliquid mass which settled to the bottom of the bag. The crude amandin was washed with water, dissolved in 10 per cent. sodium chlorid and again precipitated by dialysis. The precipitate was washed thoroughly with distilled water, increasing strengths of alcohol and absolute alcohol, and then dried in a warm room.

A considerable quantity of amandin is extracted from almonds by distilled water. A small portion thus dissolved is precipitated by dialysis and is probably extracted by the neutral salts contained in the almonds. The greater portion of the amandin dissolved in an aqueous extract, however, does not separate on dialysis but is precipitated by dilute acetic acid and is probably extracted in the form of a salt. After precipitation it shows the same gross chemical and physical properties as the amandin extracted with salt solution.

A proteose was obtained from almonds by two methods: (1) A saline or aqueous extract, which gave no further precipitate on dialysis, was dialysed against increasing strengths of alcohol and precipitated by pouring into four volumes of 95 per cent. alcohol. This crude material was purified by solution in water and reprecipitation by alcohol, which procedure was repeated three times. This method gave only a very small yield of proteose, which was explained by the fact that the proteose itself was to a great extent diffusible, in consequence of which a considerable portion was lost during the dialysis against water. (2) The second method was similar to that used in preparing ovomucoid. An aqueous extract of finely ground almonds was completely precipitated by heat and acetic acid, the filtrate concentrated and precipitated by alcohol. Purification was effected in the usual manner.[14]

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13. Osborne: Conglutin and Vitellin, Amer. Chem. Jour., 1896, xviii, 609; The Vegetable Proteins, 1909.

14. The different preparations of the proteose gave a distinct biuret reaction in dilutions of 1 to 10,000 to 1 to 15,000. A positive reaction was given to the Liebermann, Millons, xanthroproteic, Molisch and Hopkins-Cole tests. The proteose was precipitated from an aqueous solution by picric acid, potassium ferrocyanid and acetic acid, phosphomolybdic acid, phosphotungstic acid and nitric acid. The precipitates were soluble on warming the mixtures and reappeared on cooling. Tannic acid also caused a heavy precipitate, but it was not soluble on warming. Precipitation was not effected by half saturation with sodium chlorid alone but was induced by the addition of acetic acid. Acetic acid alone caused no precipitate. Partial precipitation occurred on half saturation with ammonium sulphate. The proteose was diffusible through both collodion and parchment membranes but not completely so. Prolonged dialysis always left a non-dialysable portion which responded to the proteose tests.

The results obtained with the isolated proteins from almonds when used for the cutaneous test are shown in Table 5.

TABLE 5.—TESTS WITH THE ISOLATED PROTEINS FROM ALMONDS

Solution	1-20,000	1-15,000	1-10,000	1-5,000	1-1,000	1-100
Amandin in 10 per cent. sodium chlorid or 0.5 per cent. sodium carbonate solution*	—	—	—	+	+	+u
Proteose in distilled water†	±	+	+	+u	+u	+u

*Separate tests made with preparations of amandin obtained by dialysis of a saline extract, by dialysis of an aqueous extract, or by precipitation of an aqueous extract with acetic acid gave the same results.

†Preparations of the proteose obtained by direct dialysis of ground almonds, and by methods 1 and 2, gave the same results.

The proteose from almonds was therefore capable of producing a cutaneous reaction in approximately the same dilutions as ovomucoid. The diffusible nature of the proteose explains the results shown in Table 4.

The activity of amandin was less than the proteose and was comparable to the ovomucin-globulin fraction from egg-white.

V. EXPERIMENTS WITH OATS AND OATMEAL

General.—An aqueous suspension of oatmeal or finely ground oats gave a distinct cutaneous reaction which was much less marked, however, than that obtained with almonds. The general properties of the constituents of oats on which the cutaneous reaction depended were as follows:

1. Ether and alcohol (95 per cent.) extracts of oats or prepared oatmeal applied directly or after evaporation of the solvent were inert.

2. The active constituents were completely precipitated by saturation with ammonium sulphate.

3. Oatmeal and oats were dialysed through collodion against distilled water. The dialysates for each twenty-four hours were concentrated on the water-bath and used for the skin test. The dialysates for the first five days gave a positive biuret test coincident with a distinct cutaneous reaction. The dialysates for the sixth and seventh days caused no reaction when tested on the patient and were negative to the biuret test.

4. Aqueous and 10 per cent. saline extracts of oats and prepared oatmeal were freed from protein by heat and acetic acid and by precipitation of the concentrated filtrate with alcohol. The protein-free filtrate was inert.

Experiments with the Isolated Proteins from Oats.—The globulin avenalin was extracted and purified in the same manner as amandin from almonds. Owing to the considerable amount of starch in oats a different procedure was necessary to obtain the proteose. It was prepared by two methods: (1) Oatmeal was dialysed against distilled water until the dialysates no longer gave a positive biuret test. The dialysates were

mixed, concentrated to a small bulk on the water-bath and precipitated by 95 per cent. alcohol. Purification was effected in the usual manner. (2) The proteose was found to be soluble in 50 per cent. alcohol while but a small amount of starch was removed by this menstruum. Based on this property the following procedure was used: Oatmeal or finely ground oats were extracted with 50 per cent. alcohol for twenty-four hours. The alcohol was evaporated and the remaining aqueous extract was concentrated to a very small bulk and precipitated by 95 per cent. alcohol. The resulting precipitate was purified in the usual way by dissolving in a small amount of water and reprecipitating by alcohol.

On evaporation of the 50 per cent. alcohol extract a considerable amount of the alcohol-soluble protein, *prolamine*,[15] separated out. This material was dissolved in hot 65 per cent. alcohol and precipitated by allowing the alcohol to evaporate. The precipitate was again dissolved in hot alcohol and reprecipitated by pouring into a large volume of water. This precipitate was well washed with water and 95 per cent. alcohol and dried before an electric fan. The prolamine was also obtained by extracting oats with 70 per cent. alcohol and purifying by the method given above. The three proteins from oats were used for the cutaneous test with the results shown in Table 7.

TABLE 7.—TESTS WITH THE PROTEINS ISOLATED FROM OATS OR OATMEAL

Solution	1-20,000	1-15,000	1-10,000	1-5,000	1-1,000	1-500	1-100
Globulin dissolved in 10 per cent. sodium chlorid or 0.5 per cent. sodium carbonate	—	—	—	+	+	+	+u
Proteose obtained by alcohol extraction..	—	—	±	+	+	+u	+u
Proteose* obtained by direct dialysis	—	±	+	+	+u	+u	+u
Prolamine† dissolved in 0.5 per cent. sodium carbonate or 0.5 sodium hydroxid	—	—	—	—	—	—	—

*The difference in the activity of the proteose prepared by alcohol extraction and that prepared by direct dialysis is probably due to the fact that the latter was in a purer form. It was found that the former contained some starch, while the latter was almost starch free.

†Uniform results were obtained with several different preparations of this protein.

The experiments with oats have practically the same significance as those with almonds. The active substances were closely associated or identical with the proteins. An active substance (proteose) was diffusible. The prolamine from oats was incapable of causing a cutaneous

15. Osborne: The Proteids or Albuminoids of the Oat Kernel, Amer. Jour. Chem., 1891, xiii, 327; The Vegetable Proteins, 1909.

reaction, the globulin was active in approximately the same dilutions as the globulin from almonds. The proteose from oats was slightly less active than the proteose from almonds.

VI. TESTS WITH OTHER FOODS

Various foods were used for the skin test as control experiments and also to determine whether certain substances biologically related to the toxic foods were capable of causing a reaction. The results are given in the accompanying tables.

TABLE 8.—RESULTS OF SKIN TESTS WITH VARIOUS FOODS, BLOOD SERUMS, ETC.

Food substances related to almonds (Rosaceae)		Tests with various nuts		Miscellaneous food substances	
Peach kernel	+	Brazil nut	—	Peas	—
Prune kernel	+	Pecan	—	Beans	—
Plum kernel	+	English walnut	—	Cabbage	—
Strawberry seed	+	Black walnut	—	Sweet potato	—
Apple seed	+	Chestnut	—	Irish potato	—
Pear seed	+	Butternut	—	Parsnips	—
Cherry seed	+	Hazelnut	—	Carrots	—
		Peanut	—	Cauliflower	—
Other fruit seed		Skin tests with chicken and related blood sera		Tea	—
Grape	—			Coffee	—
Orange	—	Chicken—		Milk	—
		Hen	+	Sugar	—
Food substances related to oats		Rooster	+	Bananas	+
Rice	+	Duck	+	Tests with proteins chemically related to the active proteins from eggs, almonds and oats	
Barley	+	Turkey	+		
Corn	—	Goose	+		
Wheat	—	Tests with miscellaneous blood sera		Witte's peptone (proteose)	—
Rye	+			Bence Jones protein*	—
		Lamb	—	Nucleoalbumin	—
		Horse	—	Salivary mucin	—
		Calf	—	Ovomucoid from shad roe†	—
		Pig	—	Tendomucoid‡	—
		Fish (whole blood)	—		

*Obtained through the courtesy of Dr. J. Rosenbloom of this Laboratory. "A Contribution to the Study of the Nature and Origin of the Bence-Jones Protein." Dissertation, Columbia University, 1909.

†This preparation was kindly supplied by Dr. Eddy and was prepared during previous experimental work, "On the Synthesis of Some Protein Salts." Dissertation, Columbia University, 1909.

‡One of the many preparations Prof. Gies has used in previous researches on glycoproteins.

These experiments show that the cutaneous reaction was only relatively specific and was caused by substances biologically related to eggs, almonds and oats. The reaction was produced not only by the blood-serum of the chicken, but also by that of the turkey, goose and duck. The serums of creatures not biologically related (sheep, horse, pig and cow) caused no reaction. Certain plant substances which belong to the

same family, as almonds, also caused the reaction. The results with foods related to oats were somewhat though not quite similar. Rice, barley and rye were capable of producing a mild reaction, but wheat and corn were apparently inert. On the other hand seeds of fruits and various vegetable foods which were not related to almonds or oats were incapable of causing a reaction. Bananas, however, furnish a striking exception for they caused a pronounced skin reaction. It is interesting to note that although rice, barley, rye and bananas were capable of causing a skin reaction, yet they had been eaten at various times without the production of definite symptoms.

VII. EXPERIMENTS WITH THE ACTIVE SUBSTANCES

It was demonstrated by experiments previously described that the cutaneous reaction was caused by various proteins from eggs, almonds and oats. These results indicate that the reaction was dependent on the protein substances themselves or on some substance intimately connected with them. It seemed desirable, therefore, to ascertain if possible whether the reaction was caused by the proteins themselves, or whether it was due perhaps to some contaminating substance which, though distinct from the proteins, was inseparable by the ordinary methods of preparation.

Effect of Heat.—In the preparation of the proteoses from almonds and oats and of ovomucoid, a considerable degree of heat was used which had no apparent influence on the cutaneous reaction. To determine definitely if heat had any power of impairing the reaction, the following experiments were made: Solutions of 1-to-10,000 ovomucoid and the proteoses were placed in test-tubes and immersed in boiling water for three hours. Any loss by evaporation was made up and the solutions tested on the patient, using a part of the original (unheated) solution as a control. There was no perceptible difference in the reactions.

Dialysis.—Ovomucoid and the globulins from oats and almonds did not pass through a collodion membrane and the dialysates, though concentrated to a very small bulk, did not cause a cutaneous reaction. The proteoses from almonds and oats were to a great extent diffusible through collodion and parchment membranes and the patient reacted to the dialysates as long as they gave a positive biuret test. When the dialysates no longer contained protein, no cutaneous reaction was given. At this time, however, the contents of the bag still contained a non-diffusible residue which responded to the proteose tests and was capable of causing a cutaneous reaction.

Fractional Precipitation with Ammonium Sulphate.—Aqueous solutions of ovomucoid and the proteoses from almonds and oats were precipitated by the graduated addition of ammonium sulphate. The demarcation of the different precipitates was not sharp, but from four to six fractions were obtained for each protein. Each fraction caused a cutaneous reac-

tion in dilutions of from 1 to 14,000 to 1 to 8,000.[16] The final filtrates which had been saturated with ammonium sulphate caused no reaction.

Precipitation with the Alkaloidal Reagents.—Aqueous solutions of ovomucoid and the proteose from almonds were precipitated by phosphotungstic and phosphomolybdic acids, by potassiomercuric iodid, potassium ferrocyanid and acetic acid and tannic acid. The mixtures were filtered and the filtrates used for the skin test. In no instance was a cutaneous reaction produced.

TABLE 9.—THE EFFECT OF TRYPTIC DIGESTION UPON THE ACTIVITY OF OVOMUCOID AND THE GLOBULINS AND PROTEOSES FROM ALMONDS AND OATS

Duration of Digestion, Days	Ovomucoid		Globulin Oats		Proteose Oats		Globulin Almonds		Proteose Almonds	
	Cutaneous Reaction	Biuret Reaction	Cutaneous Reaction	Biuret Reaction	Cutaneous Reaction	Biuret Reaction	Cutaneous Reaction	Biuret Reaction	Cutaneous Reaction	Biuret Reaction
7	+	+	+	+	+	+	+	+	+	+
11	+	+	+	+	±	+	+	+	+	+
13	+	+	+	+	—	+	+	+	±	+
15	+	+	+	+	..	..	+	+	—	+
19	+	+	—	+	..	..	±	+	—	+
24	+	+	—	+	..	..	—	+	..	—
46	+	+	—	+	..	..	—	+	..	..
56	+*	+	—	+	..	..	..	..	..	..
74	—	+	..	..	..	..	..	..	..	..
80	—	+	..	..	..	..	..	..	..	..

*Faint.

Adsorptive Properties.—If the active substances were chemically distinct from, but mechanically adherent to, the proteins, it was considered possible that this adsorptive tendency might be manifested by other proteins. In the effort to ascertain whether this was true, the following experiments were made:

Ten c.c. of horse's blood-serum was mixed with an equal volume of 1 to 10,000 solutions of ovomucoid and almond proteoses. The mixtures were acidulated with acetic acid and coagulated by heat. The well-washed coagulums, plain, or liquefied by artificial gastric juice, caused no reaction on the patient. The experiments were repeated using sheep instead of horse blood-serum. The results were also negative.

Effect of Tryptic Digestion.—Ovomucoid and the globulins and proteoses from almonds and oats were digested by means of an active pancreatic extract. The proteins were dissolved in 0.5 per cent. sodium carbonate solution in dilutions of 1 to 500 and 1 to 1,000 and digested at 37 C. Toluol was used as a preservative. From time to time portions of the material were removed and used for the skin test, the results of which are given in Table 9.

16. All of these precipitates contained ammonium sulphate, which accounts for the fact that they gave the reaction only in more concentrated solution than the pure proteins.

These experiments showed that the activity of the proteins was destroyed by tryptic digestion and that the cutaneous reaction disappeared before the proteins were completely hydrolysed. It seemed, therefore, that the cutaneous reaction was dependent on some grouping of the protein molecule higher than the peptones. In order to determine this point with greater accuracy the globulins from almonds and ovomucoid were subjected to tryptic digestion for fifteen days, at which time the mixtures were capable of producing a marked reaction. No precipitate was produced by neutralization with hydrochloric acid. The substances precipitated by saturation with ammonium sulphate produced a marked skin reaction; the filtrate gave a distinct biuret reaction but produced no effect when tested on the patient.[17]

These experiments demonstrate that the substances responsible for the cutaneous reaction partook of the general properties of the proteins and that it was impossible to obtain an active substance distinct from the proteins. On gradual hydrolysis of the active proteins with trypsin the cutaneous reaction disappeared before the biuret reaction. So far as one can judge from these experiments it seems probable that the cutaneous reaction was dependent on some definite grouping in the protein molecules.

VIII. THE NATURE OF THE PATIENT'S HYPERSUSCEPTIBILITY

The next problem of importance concerned the nature of the patient's idiosyncrasy. Obviously his hypersusceptibility to the food proteins was due to one of two causes. Either he lacked some protective substance which is present in normal individuals, or he was sensitized in some way to the food proteins.

A number of experiments were undertaken in the effort to demonstrate the presence of a protective substance in normal individuals. Four specimens of human blood (citrated) and human blood-serum were mixed with different dilutions of the active proteins and tested on the patient immediately or after incubation at 37 C. In no instance did these solutions give a less active cutaneous reaction than the controls which were of the same dilution but did not contain blood or serum. Moreover, the minimum dilution of the active substances necessary to induce the cutaneous reaction was entirely independent of the presence of human blood or serum in the solutions.[18]

17. Results obtained by hydrolysis with 25 per cent. sulphuric acid were practically identical with those obtained by tryptic digestion.

18. The attempt was also made to determine whether the patient's blood contained some substance which by its action on or combination with the active proteins was capable of producing urticaria. Mixtures of the patient's blood and blood serum in different proportions with varying dilutions of ovomucoid and the proteoses from almonds and oats were tested on normal individuals. The tests were made immediately after mixing and also after varying periods of incubation at 37 C. In no instance was urticaria produced.

These experiments being entirely negative, the attempt was made to sensitize passively guinea-pigs to egg my means of the patient's blood-serum. The results of the experiments are shown in the following protocols:

1. A 260 gm. guinea-pig was given 6 c.c. of partially inactivated[19] blood-serum from the patient by intraperitoneal injection. Twenty-five hours later 150 mg. of ovomucoid by intraperitoneal injection. The development of symptoms was as follows: 15 minutes after injection, coat roughened, animal uneasy. Twenty minutes: cough, stridor, recession of sides on inspiration, slight diarrhea. Twenty-five minutes: dyspnea increasing, tendency to lie on side. Forty-five minutes: body limp, respirations labored. Apnea and death 82 minutes after injection. Autopsy: Lungs whitish and enormously distended leaving but a small triangular area of the heart uncovered, petechial hemorrhages in intestinal wall. Heart continued to beat over 10 minutes after the thorax was opened.

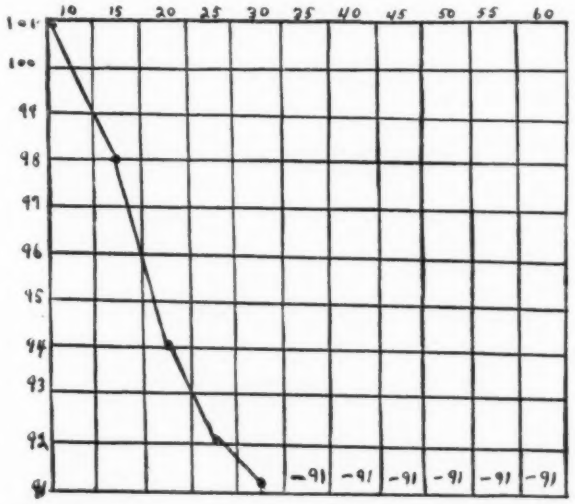

Chart 1.—Temperature Curve of Guinea-Pig 1. Figures at the left indicate the temperature F. The thermometer was not graduated below 91 F. The figures at the top indicate minutes after the injection.

2. Weight 290 gm.; 6 c.c. of partially inactivated blood serum from the patient by intraperitoneal injection; twenty-nine hours later 150 mg. of ovomu-

19. In the first experiments the attempt was made to inject the blood-serum in active form. The active serum was extremely toxic for guinea pigs, 3 c.c. being sufficient to cause the death of a 250 gm. pig within eight to ten hours. The serum was then partially inactivated by heating at 53 to 54 degrees C. for sixteen minutes. After this treatment the serum still caused the animals to become slightly ill (roughening of coat, lachrymation, slight dyspnea), but they recovered completely within a few hours. The toxic action of normal blood-sera has been studied by Uhlenhuth, Pfeiffer (Ueber die nekrotisirende Wirkung normaler Seren, Ztschr. f. Hyg. u. Infektionskr., 1905, li, 183; ibid. Wien. klin. Wchnschr., 1909, xviii, 465; Das Problem der eiweiss Anaphylaxie, etc., 1910) and others and is considered due to a definite antibody, probably hemolytic. According to Pfeiffer the symptoms due to the injection of toxic foreign sera are practically identical with those of anaphylaxis.

coid (in normal saline) by intraperitoneal injection. Fifteen minutes: animal uneasy, roughening of coat; 25 minutes: Dyspnea, recession of sides on inspiration, cough; 45 minutes: body limp, lying on side; respirations slowed and labored; began to improve about an hour after the injection and had recovered completely in about five hours.

Controls.—Four guinea-pigs about 250 gm. in weight each, were given 6 c.c. of normal human serum (partially inactivated) by intraperitoneal injection. Twenty-four hours later three were given 150 mg. of ovomucoid by intraperitoneal injection. Beyond a fall of temperature of 1 to 3 degrees F. they developed no symptoms. The remaining animal was given 2 c.c. of inactivated horse serum by intraperitoneal injection. No symptoms developed.

These experiments demonstrate that the patient's blood-serum contained some substance which was capable of sensitizing guinea-pigs to ovomucoid. It seems justifiable to assume therefore that the allergic condition of the patient — to egg at least — was due to protein sensitization or anaphylaxis.[20]

IX. IMMUNIZATION. THE RELATIONSHIP OF THE PATIENT'S ALLERGY TO EGGS, ALMONDS AND OATS

The next, and the most important problem from a practical standpoint, was that of immunization.[21] The patient's marked idiosyncrasy to egg was, to say the least, a great inconvenience. A vast amount of care was required in the preparation and supervision of his food and a number of palatable and nutritious food preparations were excluded from his dietary. With the problem of immunization was also connected several points of scientific interest.

The history of the patient indicates that his idiosyncrasy to egg was not congenital but was acquired at some time when he was between the ages of 10 days and 14 months. It seems possible that sensitization occurred at the time egg was first administered. In reference to oatmeal the history is similar. The first administration of oatmeal when the patient was 22 months old caused no symptoms; subsequently the ingestion of oatmeal caused characteristic urticarial lesions.

On the other hand, so far as can be ascertained from the history, toxic symptoms occurred the first time almonds were eaten. To explain his

20. These experiments have a close analogy to those of Bruck (Experimental Beiträge zur Aetiologie und Pathogenese der Urticaria, Arch. f. Dermat. u. Syph., 1909, xcvi, 241). The patient was susceptible to urticaria from the ingestion of pork. Bruck was able to sensitize guinea-pigs to pig's serum by means of injections of the blood-serum of the patient. The experiments were admirably controlled and were conclusive in every way.

21. The only recorded instance of immunization in a case of idiosyncrasy to egg that I have been able to find is that of Scofield (A Case of Egg Poisoning. Lancet, London, 1908, i. 716) whose patient suffered from disturbances practically identical with those of my own patient. Scofield began by administering minute quantities of egg in pills (1-10,000 part of a raw egg), gradually increased the dose and later gave foods containing small amounts of egg. By this means the patient was cured of the idiosyncrasy.

hypersusceptibility to almonds three possibilities were suggested: (1) The condition may have been congenital; (2) the patient may have been sensitized by eating a small amount of almonds, which circumstance escaped the observation or memory of the parents, though this seems most unlikely; (3) the sensitization to eggs or oats may have in some way rendered him hypersusceptible to almonds. There would be no means of ascertaining whether the first or second hypothesis was correct. From the results of immunization, however, evidence could be obtained which would serve to show the correctness of the third hypothesis.

It seemed preferable therefore to use a single protein for immunization rather than any one or all of the three foods, as by this means it could be ascertained whether the patient's hypersusceptibility to the different proteins and foods was in any way related. If, for example, immunization to one protein from the egg also induced immunity to the other active

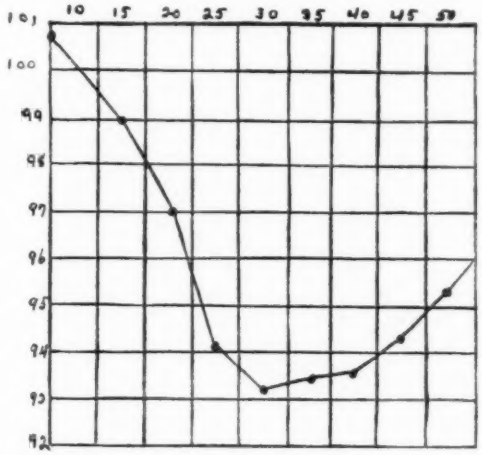

Chart 2.—Temperature curve Guinea-Pig 2. The figures at the left indicate the temperature F. The figures at the top indicate the numbers of minutes after the injection.

protein from this source, it would show that the patient was not sensitized to the distinct proteins but to some constituent group common to both. If immunity to almonds and oats also occurred, proof would be ample that the patient's allergic condition was specific neither for the protein molecule as a whole nor for the proteins of a single source, but to some group common to the active proteins of all three foods.

On the other hand, if immunity was induced only to the protein administered, or to proteins of the same source, a separate sensitization to each protein, or to each food, must be assumed.

Ovomucoid was selected as the protein for immunization, as it was one of the most active and could be prepared easily and in a state of comparative purity.

Treatment was begun Oct. 28, 1911, by the administration of 2 mg. of ovomucoid in capsules three times a day. The dose was increased at first gradually and then more rapidly. At first the quantity was increased at the rate of 2 mg. a day and on November 19 the daily increase was raised to 6 mg. Subsequently the daily increase was as follows: from November 26 to December 5, 12 mg.; from December 5 to December 14, 24 mg.; from December 14 to December 23, 48 mg.; from December 23 to January 1, 78 mg.; from January 1 to January 14, 190 mg.; from January 14, 380 mg. Toward the end of immunization the patient was taking over 7 gm. of ovomucoid a day.

The progress of immunization was determined by means of the cutaneous reaction. About the first of December the reaction began to decrease and was induced only by comparatively strong dilutions of ovomucoid, 1 to 500 and stronger. On January 8 the reaction had decreased greatly and on January 11 a small amount of egg-white was touched to the patient's lips. No disturbance occurred and on January 12 the patient ate about one-sixth of an egg with no ill effect.

From this time foods containing egg, and also soft boiled or raw eggs, were fed each day. The foods containing egg caused no symptoms. At first the patient complained that soft boiled egg caused his mouth to sting or itch but these sensations were accompanied by no objective disturbances and later disappeared. During the immunization the patient was in comparatively good health and presented no symptoms referable to the administration of the ovomucoid. The larger doses of ovomucoid, however, produced a fall of temperature which was most pronounced after a marked increase in the dose and at times amounted to 1.8 F. This fall of temperature would gradually become less pronounced. When the dose was again greatly increased the fall of temperature would recur.

The cutaneous reaction to egg and the proteins from egg has entirely disappeared. The proteose from oats causes no reaction in dilutions as great as 1 to 50 and oatmeal has been eaten a great number of times with no resulting symptoms. A distinct cutaneous reaction is still given to a 1 to 500 dilution of almond proteose. A 1 to 100 dilution is capable of causing urticaria by contact with the unbroken skin. Dilutions weaker than 1 to 1,000, however, cause no cutaneous reaction. The decrease in the patient's reaction to this substance is shown by comparison with the results in Table 5. Almonds have been eaten several times; in most instances the patient complained of itching of the tongue or throat, but usually nothing was visible on examination. On two occasions, however, urticarial wheals appeared on the inner surface of the lower lip. This disturbance appeared to be less than that which occurred previous to immunization. A differential blood count on February 7 was as

follows: polynuclear cells, 64 per cent.; mononuclear cells, 27.3 per cent.; eosinophils, 8.1 per cent.; mast cells, 0.2 per cent.

The above experiments showed that the administration of ovomucoid by mouth completely immunized the patient to egg. It is therefore apparent that he was not sensitized to the distinct proteins of the egg but to some constituent group common to the toxic proteins. At the same time the patient became entirely immune to oatmeal and less sensitive, though not immune, to almonds. Judging from these results it would seem that the patient's allergic condition to the three dissimilar foods was in some way related. Our present knowledge of the subject is too meager, however, to interpret these results as proving that the original sensitization to egg or oats also sensitized the patient to almonds. Moreover, the results from a single case are insufficient data on which to base this view, which is not in accord with the current ideas of the specificity of anaphylaxis.[22] Another possibility which must be considered is that the sensitization to egg and oats, although not the direct cause of the patient's idiosyncrasy to almonds, may have served in some way as a predisposing cause.

X. SUMMARY

In a boy now 8 years old marked urticarial lesions were caused by the ingestion of eggs, almonds and oatmeal. The idiosyncrasy to egg was not congenital but was acquired at some time between the ages of 10 days and 14 months. Symptoms due to the ingestion of oats appeared some time after the child had first eaten oatmeal when he was 22 months old. As far as can be ascertained, the idiosyncrasy to almonds was manifested the first time this food was eaten.

It was found that cutaneous inoculation of these and certain related food substances produced an urticarial wheal at the site of inoculation. The cutaneous reaction was produced only by the protein constituents of eggs, almonds and oats. Different proteins from the same source varied in activity, some being incapable of causing a reaction. Some of the active proteins caused urticaria by mere contact with the unbroken skin.

It was possible passively to sensitize guinea-pigs to ovomucoid (one of the active proteins from eggs) by intraperitoneal injections of the patient's blood-serum.

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22. Our present knowledge of anaphylaxis, however, is derived almost entirely from animal experiments and there is no proof that the specificity of the phenomenon is the same for all species. It is quite possible that the reaction in man is not specific, and other cases of food allergy which are under observation at the present time support this view. On the other hand, it is also possible that there is some fundamental condition present in certain individuals which may predispose to sensitization by food substances. If this were true the individual may be sensitized separately to each food to which he reacts and the non-specificity of anaphylaxis in the human being may be only apparent and not real.

By feeding ovomucoid in gradually increasing doses the patient became immune to egg. At the same time immunity to oatmeal and an apparently decreased susceptibility to almonds occurred.

I wish to acknowledge my deep indebtedness to Professor Gies for his kindness in placing the facilities of his laboratory at my disposal, and to him and his associates for much assistance. It is a pleasant duty to express my thanks to the parents of the patient not only for their patience and cooperation during ten months of tedious experimentation, but also for a number of valuable observations.

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THE WASSERMANN REACTION IN INFANTS AND CHILDREN: A CLINICAL STUDY*

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The diagnosis of early congenital syphilis as a rule is not difficult. The diagnosis of the same disease in later childhood is often a matter of great difficulty. Careful inquiry into the history, both family and personal, may throw no light on the case, and the characteristic signs which would enable one to make a diagnosis may be slight, or entirely absent; yet, later, perhaps at the age of puberty, such signs do arise and the diagnosis is evident. Undoubtedly such cases are syphilitic from the onset, but run a "latent" course, perhaps for several years, and then under certain conditions break out in a more pronounced form.

The diagnosis being thus at times difficult, any measures leading to ease and certainty of detection are eagerly welcomed. Studies of recent years have given us three such measures: the detection of the *Spirochæta pallida* in the secretions or tissues of the body, inoculation experiments on monkeys or rabbits, the serum reaction of Wassermann. While the clinical diagnosis will continue to be the most important method in the future, as it has been in the past, these other recent methods will be of great value especially in obscure, latent cases. Of these methods the serum reaction is the most widely used and of the greatest practical value. This method depends on the complement-uniting reaction first described by Bordet and Gengou in 1901. In 1905 Wassermann applied this reaction to the diagnosis of syphilis.

"The reaction depends on the fact that serum from a positive syphilitic patient contains certain reaction bodies or antibodies which, in the presence of a known antigen from the liver of a syphilitic fetus, combines with the complement. The complement being bound in this first step, does not enter into combination with the hemolytic system, which is the indicator in the reaction, and therefore hemolysis is prevented, or inhibition of hemolysis occurs, giving a positive reaction. If the serum of a normal person is brought into combination with a known syphilitic antigen, derived in the same way as above, there is no union with the complement, which consequently is left free to unite with the hemolytic system, the indicator again, and hemolysis does occur, giving a negative reaction."

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*From the Children's Memorial Hospital.
*Read before the New England Pediatric Society, March 30, 1912.

In most of the tests made in this series, the Noguchi modification of the Wassermann method has been used. It is not the intention of this paper to enter into a discussion of the relative merits of Wassermann's original method and Noguchi's modification thereof. The evidence seems conclusive, to a clinician at least, that the Noguchi method is fully as reliable as, and perhaps more sensitive than, the Wassermann technic, and yet in the hands of an expert is not too sensitive, i. e., does not give positive results in non-syphilitic cases (Kaliski). It furthermore has the advantage of requiring less blood, a factor of no little importance in carrying out the technic in small children.

TECHNIC

The various steps are as follows: The blood may be obtained from either a vein or, preferably, from a finger or the great toe; only about 1 c.c. is required; to obtain this a finger or the great toe is punctured with a Hagedorn needle, the part massaged toward the puncture and the blood collected in a Wright capsule (Fig. 1). "The straight empty end of the tube is now sealed with a flame, cooled, shaken to drive the blood from the bent end to the straight sealed end, and the bent end is then sealed in the flame. Care must be taken not to apply the heat to the blood itself. After sealing, the tube may be mailed to the serologist for examination. Wright's capsules may be made by drawing out ordinary thin glass tubing in the flame of an alcohol lamp or Bunsen burner.

"The blood clot and the serum separate in a few hours at room temperature. If the test is not made within two or three days, the serum should be drawn off with a capillary pipet; otherwise, if left in contact with the clot, it will become tinged with the hemoglobin and this will somewhat interfere with the accurate reading of the test" [1] (Fig. 2).

The spinal fluid may be used for the test in cases in which a lumbar puncture is done for either diagnostic or therapeutic purposes, or in certain cases of emaciated, atrophic infants where it seems impossible to obtain enough blood and where a test is imperative; in the latter class of patients a lumbar puncture may be done especially for this purpose. It must be borne in mind, however, that in a small proportion of cases, the spinal fluid will give a negative reaction, when the blood gives a positive one.

DIAGNOSTIC VALUE OF SERUM TEST

The Wassermann test has now been applied to thousands of cases of undoubted syphilis in adults, has been found present in from 60 to 100 per cent. of the cases, according to the stage of the disease, and is universally accepted as of great diagnostic value. The test has also been applied

1. Noguchi: Serum Diagnosis of Syphilis, ed. 2, 1911, p. 54. Lippincott Co., Phila.

to syphilitic infants and children, though in smaller numbers, and among them also is regarded of great diagnostic significance. Various observers — Mulzer and Michaelis, Bauer, Halberstaedter, Muller and Reiche, Reinhart, Stroscher and others — applying the test to cases of manifest, undoubted syphilis, find it positive in from 96 to 100 per cent. of the cases. There can be no doubt of its diagnostic value then in early as well as in later life.

But most of these observations have been made on cases of undoubted syphilis, cases in which the clinical signs left no doubt of the nature of the disease. Those making the observation have been engaged in "testing" the test, to see if it would "ring true"; to see if it would coincide with the clinical picture of well-known, easily recognized cases of the disease. They have proved beyond a doubt that the test does "ring true," that it does react positively in practically all cases with manifest signs of early congenital syphilis — "snuffles," skin lesions, mucous membrane lesions, etc. Indeed, in the very early cases, the reaction is apt to run closely hand-in-hand with the clinical signs; thus Mulzer and Michaelis report cases with suspicious family records, but themselves without physical signs, who gave soon after birth a negative serum reaction, and later, just before, or coincidently with, the breaking out of characteristic signs, a positive reaction.

The use of the test, however, in other groups of cases, those of the obscure or latent type, as a valuable aid in determining the presence or absence of a syphilitic taint, has been little practiced. Comparatively few applications of the test have been made to cases which might be syphilis, yet are without sufficiently well-defined physical signs to warrant a positive diagnosis. One finds but few large series of these indefinite cases. Isolated examples of this or that condition are reported with either a positive or negative reaction, but not in sufficient number in a particular condition, e. g., arthritis, to justify conclusions as to the frequency of syphilis as a foundation cause of that condition.

Certain affections of the nervous system, however, have been studied with the test. Thus Knopfelmacher and Schwalbe, studying the Wassermann reaction in hydrocephalus, collected twenty-nine cases, eight of which were positive (27 per cent.). They also quote some Danish workers who, among 2,000 cases of mental deficiency, practically all adults, found thirty-one giving a positive reaction. This series included 259 epileptics, only one of whom was positive.

Dean tested 330 cases, children or young adults, in a Potsdam asylum, and found positive results in fifty-one (15 per cent.). The most of these were idiots; they formed the bulk of the positive cases, forty-four of the fifty-one being in this class of patients. He also brings out the significant facts that of the fifty-one positive cases, only nine were clinically syphilis, four were suspected cases, and thirty-seven were entirely without signs of

the taint. Furthermore, he found that the proportion of positive cases diminished rapidly after 16 years of age, and suggests that a large percentage of positive results might be obtained in younger children. Dean quotes various authors, Ravait, Breton, Petit and Gayetoe, who have studied similar cases and have found from 9 to 30 per cent. giving a positive reaction.

Cases illustrating other conditions have been tested in but small numbers. They serve only to emphasize the fact that "symptomless" infants and children may give a positive reaction. Such are mostly very young infants, the offspring of parents known to be syphilitic; e. g., the cases already cited (Mulzer and Michaelis), also cases mentioned by Hochsinger: infants in whom the physician has reason to suspect a syphilitic inheritance and therefore has performed the serum test.

FIELD OF APPLICATION

There is a wide field for the use of the Wassermann serum test, as yet but little explored, in that class of patients frequenting our dispensaries and hospital wards. No extensive investigations of the serum test on a broad and comprehensive scale have yet been carried on among these patients. We are all familiar with the type: anemic, undersized, with lymph-nodes generally enlarged, often with a high lymphocyte count, they are generally below par, perhaps degenerate, and present a condition due to a great variety of causes, one of which *may* be syphilis. It is in this type of cases especially that the Wassermann test may be of great value, for its presence in such children is very strong evidence pointing toward a syphilitic foundation for their deteriorated, degenerate condition; its absence almost certain proof that syphilis does not exist.

OBJECTS OF THE PRESENT STUDY

It is with this class of children that this paper deals. The present study has been undertaken to determine, as far as possible, the following points:

1. What proportion of our hospital children will show a positive serum reaction?

2. What proportion of the positive cases present signs suggestive of syphilis?

3. Does a positive serum reaction in a child without characteristic physical signs mean syphilis?

The tests in the present series were made by Drs. W. E. Post, J. F. Waugh and H. K. Nicoll, and I wish to express my deep appreciation for the courtesy and skill of these gentlemen in thus making the work possible. Though not connected with the Hospital, they have given freely of their time and thought purely from "love of the cause" and interest

in an investigation which they as well as myself believe to be worth while, indeed even necessary. The work would have been impossible without their generous cooperation.

Tests were made on 102 infants and children, on six mothers and two fathers. On the children, 111 tests in all were made, twenty-eight Wassermann, eighty-three Noguchi. The blood was used in ninety cases, the spinal fluid in twelve cases. The children ranged in age from 3 days to 12 years; all, with but two exceptions, were patients at the Children's Memorial Hospital. There were thirty-nine positive reactions, sixty-two negative, and one case with a positive Noguchi but negative Wassermann. Thus 38 per cent. of the cases gave a positive reaction.

The mothers of the children in four positive cases were tested and gave one negative and three positive reactions; the one with the negative reaction had had the last one of three miscarriages two years before the test was made; she had had no specific treatment. The mothers of two negative-reacting children both gave negative results. Of the two fathers, one, with a positive-reacting child, himself gave a positive result. The second father was the parent of the 18-months-old infant with a positive Noguchi and negative Wassermann reaction and gave two negative Wassermanns, done by two different serologists a few days after the child was tested. No Noguchi was done on the father.

None of the 100 children entered the hospital as a case of syphilis. The admissions diagnoses are given in Table 1.

We note the great variety of diseases represented, involving practically all of the different systems of the body: nervous, circulatory, bony, respiratory, etc. But the affections which most attract attention by their positive results are those involving the nervous and circulatory systems, and the tuberculous infections. There are seventeen cases presenting diseases of the nervous system, with nine positive and eight negative reactions; sixteen cases of heart trouble, with seven positive and nine negative, and twenty-six tuberculous cases, with eight positive and eighteen negative reactions. There are fifteen cases affecting the respiratory system, five positive and ten negative. The remainder are scattered among the various conditions represented in Table 1. This table shows the varied character of the cases tested and also the proportion of positive cases. The number of cases, however, in a given condition is so small that the percentage of positive cases in such given condition cannot be considered as by any means an average percentage; this can be determined only by future investigations when large numbers of cases have been tested and analyzed.

Our chief interest of course is in the positive cases. These will now be considered in groups by themselves.

TABLE 1.—GIVING A SYNOPSIS OF ADMISSION DIAGNOSIS AND REACTIONS IN ALL CASES

Admission Diagnosis	Totals	Positive	Negative	Per cent. Positive
Tuberculosis—				
General	3	2	1	..
Meningeal	4	1	3	..
Pulmonary	2	1	1	..
Joints	17	4	13	31
	26	8	18	
Nervous System—				
Brain tumor	1	1	0	..
Little's disease	3	1	2	..
Encephalocele	1	0	1	..
Meningitis (meningococcus)	1	0	1	..
Meningitis, chronic	1	0	1	..
Microcephalus	1	1	0	..
Amaurotic family idiocy	1	1	0	..
Epilepsy	4	2	2	..
Spinal cord lesion	1	1	0	..
Poliomyeloencephalitis	2	1	1	..
Miscellaneous	1	1	0	..
	17	9	8	
Circulatory System—				
Congenital heart	5	2	3	40
Chronic endocarditis	11	5	6	45
	16	7	9	
Respiratory System—				
Rhinitis	1	1	0	..
Tonsils and adenoids	8	3	5	37
Bronchitis	1	0	1	..
Pneumonia	4	1	3	..
Asthma	1	0	1	..
	15	5	10	
Digestive System—				
Hare-lip	5	1	4	20
Enteritis	5	1	4	20
	10	2	8	
Osseous System—				
Arthritis periostitis	1	1	0	..
Osteomyelitis	1	1	0	..
Club-foot	2	0	2	..
Fractured toe	1	0	1	..
	5	2	3	
Miscellaneous—				
Anemia	2	1	1	..
Keratitis	3	2	1	..
Phimosis	1	1	0	..
Rachitis	5	1	4	20
Still's Disease	1	1	0	..
Typhoid fever	1	0	1	..
	13	6	7	
Totals	102	39	63	38

POSITIVE CASES

The total number of cases giving a positive reaction is thirty-nine, ranging in age from 1 week to 12 years, distributed as follows:

Age, Years	No. of Cases	Age, Years	No. of Cases
Under 1	5	7	4
Between 1 and 2	4	8	3
2	1	9	4
3	4	10	2
4	4	11	3
5	2	12	2
6	1		

There were twenty-five boys and fourteen girls.

METHOD OF STUDY

The cases have been studied from the following points of view: the admission diagnosis, the family history, the patient's own previous record of development and general health, the physical condition at the time of making the test, and, in the fatal cases, the results of autopsy. Information along these lines seemed necessary in order to "check up" the test and to answer the second and third questions. Details of the cases are given in Table 3.

The admission diagnoses are given in Table 2. Study of this table shows that of the thirty-nine positive reactions, 8 were obtained in tuberculous trouble, 9 in affections of the nervous system, 5 respiratory, 7 circulatory, 2 osseous, 2 digestive, and 6 were in miscellaneous conditions.

The family history was investigated with special reference to syphilis. It shows a positive record of this disease in four cases, a suggestive record in sixteen cases, a negative one in eighteen cases, no history obtainable in two cases. By a "positive" record is meant a definite history of clinical syphilis in another member of the family or a positive Wassermann reaction in either parent; by a "suggestive" record is meant a history of miscarriage in the mother, of serious mental or nervous trouble in another member of the family, or the occurrence of a positive reaction in a brother or sister not of adult age. Thus, of the thirty-nine cases twenty-one (56 per cent.) show a family history conclusive or suggestive, of a syphilitic taint. Only 20 per cent. of the negative cases show such family history.

The family history is often such an important factor in arriving at a diagnosis of congenital syphilis, that it has seemed worth while thus to consider it by itself with reference to the serum reaction in the positive cases. But the personal record and the physical condition of the child himself must, after all, finally determine the question. The cases, therefore, have been studied with reference to the combination of all three of

TABLE 2.—ADMISSION DIAGNOSES IN THE POSITIVE CASES

	No. of Cases
Tuberculosis—	
General	2
Joints	4
Meningeal	1
Pulmonary	1
Total	8
Nervous System—	
Brain tumor	1
Little's disease	1
Microcephalus	1
Amaurotic family idiocy	1
Epilepsy	2
Spinal cord, lesion of?	1
Poliomyeloencephalitis	1
Miscellaneous nervous	1
Total	9
Respiratory System—	
Rhinitis	1
Tonsils and adenoids	3
Pneumonia	1
Total	5
Circulatory System—	
Congenital heart	2
Chronic endocarditis	5
Total	7
Osseous System—	
Periostitis	1
Osteomyelitis	1
Total	2
Digestive System—	
Hare-lip, etc.	1
Enteritis	1
Total	2
Miscellaneous—	
Anemia	1
Keratitis	2
Phimosis	1
Rachitis	1
Still's disease	1
Total	6
Grand Total	39

these factors, i. e., family history, personal record and physical examination, in order to see to what extent these factors and the serum reaction coincide. For this purpose they will now be rearranged in five separate groups.

Group I.—Cases with family history, personal record and physical signs, all suggestive, or even diagnostic, of syphilis. There are nine of these cases.

Group II.—Cases with either family or personal history, plus physical signs, suggestive of syphilis. There are nine of these cases.

Group III.—Cases with only physical signs suggestive of syphilis. There are six of these cases.

Group IV.—Cases with either a suggestive family history alone, or a suggestive personal record alone. There are five of these cases.

Group V.—Cases without either family history, personal record or physical signs suggestive of syphilis. There are ten of these cases.

The cases of Groups I, II and III may all be regarded as clinically syphilis. All of these, twenty-four in number, or 63 per cent. of the positive cases, give suggestive physical signs. Among the negative cases only 5 per cent. give such suggestive signs. Cases of Group IV, in view of either a positive family history or positive personal record plus a positive serum reaction, are probably syphilitic, making in all, twenty-nine cases, or 28 per cent. of the whole series, which are probably syphilis.

Group V is an important group and requires special discussion, but before proceeding with that discussion, certain cases in the other groups are of interest.

Group I.—Cases 26 and 27 were twin brothers who entered the Hospital for the removal of tonsils and adenoids. Both were undersized though of different weights; each had a goiter. The mother had had three miscarriages since the birth of the twins but gave, at this time, a negative Noguchi reaction. The twins were put on mercurial treatment, Nov. 11. 1911, and began to improve immediately, the more vigorous one faster than his brother; the former went from 52½ pounds, Feb. 16, 1912, up to 54½ pounds, March 23, 1912, and on the latter date had a negative reaction; his brother, between the same dates, went from 50 pounds to 51½ pounds and still gave a positive reaction. The more vigorous one of these twins thus gave evidence of greater resistance to his hereditary taint, not only by the improvement in his general physical condition, but by the change of his positive reaction into a negative one.

Cases 35 and 36 were also brothers, instances, again, of "familial" syphilis, each showing a keratitis, one also an arthritis and one also deafness. Both left the hospital unimproved after three weeks' treatment with mercurials; five months later the arthritis one returned with his keratitis much worse and his serum reaction still positive. He is now under observation, improving under vigorous mercurial treatment.

Group III.—Case 34 was an anemic, 18-months-old infant in private practice; she was backward about her teeth, was fat and "flabby," had a lymphocytosis and a dactylitis. Her blood gave a markedly positive Noguchi reaction. One of the leading syphilographers of Chicago saw her with me in consultation, could not accept the specificity of the Noguchi reaction, doubted the diagnosis of syphilis, and suggested a

straight Wassermann test. This was done and was reported negative. Calomel, one-tenth gr. t. i. d. for four days had been given after the Noguchi and before the Wassermann test, but it is improbable that this small amount of mercury converted a positive into a negative reaction. The tests were done by different serologists, both skilful and expert workers. The father was an educated man, appreciated the importance of the truth, denied syphilis, and his blood gave a negative Wassermann reaction, the test being made by the man who found the negative reaction in the child. No Noguchi was done on the father.

GROUP IV.—Case 3, a 3-year-old child, entered the Hospital as a case of tuberculous meningitis. The father gave a history of "soft" chancre seven years before (i. e., four years before the birth of the patient), the mother a history of one miscarriage (date ?); and of a baby younger than the patient who had always been "delicate with heart trouble" and who died at 1 year. The patient's spinal fluid gave a strong Noguchi reaction. The autopsy showed a marked tuberculous meningitis, with tubercle bacilli present in great numbers in the exudate at the base of the brain. There were no lesions of syphilis, either gross or microscopic; no spirochetes in the meningeal exudate examined by the Levaditi method. The head only was examined.

GROUP V.—The cases of this group cannot be regarded as clinically syphilis in the ordinary sense of the term, and such a diagnosis would rest largely on the results of the serum test; in these cases the test was positive. Are we, then, to accept such a result as evidence of the presence of syphilis? Are we to regard as cases of syphilis, patients who, without suspicious family history, without suggestive personal record or physical signs, yet nevertheless give a positive serum reaction? How are we to explain the positive reaction in such patients?

There are three possible explanations:

1. The reaction is correct and is due to some condition other than syphilis.

2. The reaction is correct and is due to syphilis, which may be the real underlying cause of the condition named, or may be a factor predisposing toward some other infection, e. g., tuberculosis.

3. The reaction is incorrect, due to some error of technic.

The first supposition, that the reaction is due to some condition other than syphilis, is untenable. Aside from syphilis, the only conditions in which a positive Wassermann reaction has been found are scarlet fever, jaundice, leprosy, carcinoma, diabetes mellitus and possibly malaria. None of these conditions existed in any of the cases in Group V; furthermore, there is no ground for believing that any of the conditions named in this group would cause a reaction of such specificity as is the Wassermann reaction.

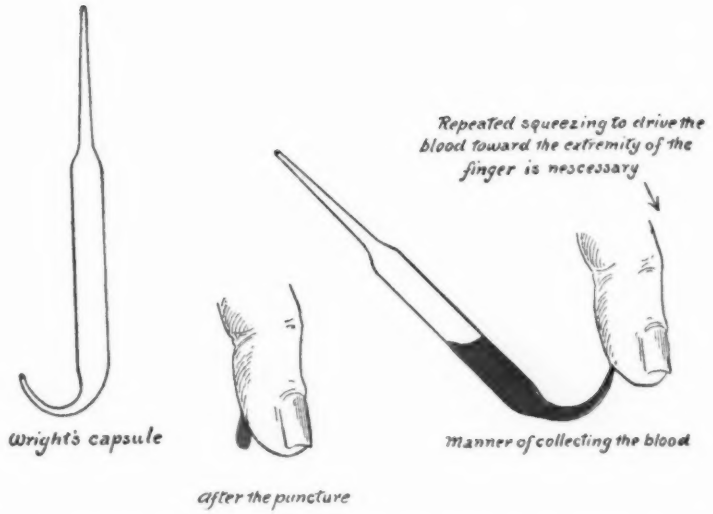
Repeated squeezing to drive the blood toward the extremity of the finger is necessary
Wright's capsule
Manner of collecting the blood
After the puncture

Fig. 1.—Method of collecting blood from the finger-tip by means of a Wright capsule. (From Noguchi: The Serum Diagnosis of Syphilis, 1912.)

Illustrating Article by
Dr. F. S. Churchill, Chicago, Ill.

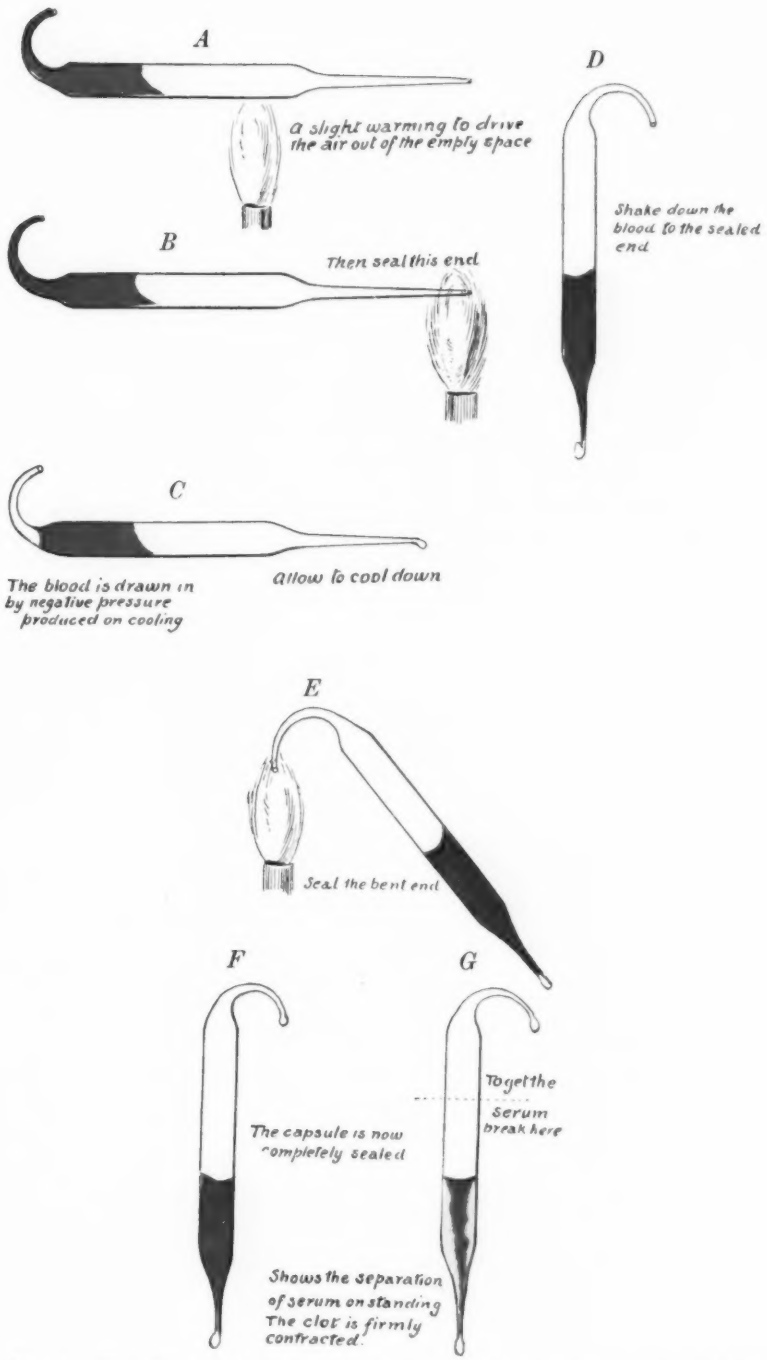
A
A slight warming to drive the air out of the empty space
B
Then seal this end
C
The blood is drawn in by negative pressure produced on cooling
Allow to cool down
D
Shake down the blood to the sealed end
E
Seal the bent end
F
The capsule is now completely sealed
G
To get the Serum break here
Shows the separation of serum on standing The clot is firmly contracted.

Fig. 2.—Showing the further steps in the technic of collecting the blood and obtaining the serum in the serum test for syphilis. (From Noguchi: The Serum Diagnosis of Syphilis, 1912.)

The second supposition, that the reaction is correct and is due to syphilis, the physical conditions found being either unusual manifestations of syphilis or coexisting as separate entities, e. g., tuberculosis, is debatable.

Syphilis is of course a most protean disease. Not a single tissue of the body is there that may not be attacked by the virus, once the latter has gained access to the body. Its obscurity and latency at times are well known. Especially in congenital syphilis may its manifestations be most varied. They may furthermore be latent for a period, giving rise to no symptoms or signs, yet later showing characteristic stigmata of the disease, the so-called *syphilis hereditaria tarda.* It is conceivable that the cases in Group V may belong to this class; that they are cases of latent, late syphilis and that they may show active signs of the disease later on in life, perhaps at puberty. Before the advent of the serum test it would not have occurred to any clinician examining these patients to regard them as syphilitic. He would have classified them as above, and their anemia, lymphocytosis, adenitis and general deterioration he would have attributed to general causes — bad hygiene, bad food, lack of care, etc. But among the causes to which these conditions *may* be due is the specific cause syphilis; hence, finding these conditions present, finding also present a test so strongly diagnostic of syphilis as is the serum test, it is entirely possible that these cases in Group V may be syphilitic, that they are in reality cases of hereditary syphilis, in a latent stage; cases in which the disease process is so sluggish that it has as yet given rise to no gross, evident sign characteristic of the taint, yet active enough to produce a more or less deteriorated condition and a positive result when tested by the delicate serum reaction.

This reasoning, however, cannot, I believe, apply to the three fatal cases in the group, Cases 12, 31 and 38. Cases 31 and 38 came to autopsy and showed no signs gross or microscopic of syphilis. No spirochetes were detected in the liver in either case. The heart muscle was not examined for the spirochetes, and it is possible, in view of recent investigations, notably by Warthin, that they might have been found in the tissues of that organ. The third fatal case, Case 12, was one of amaurotic family idiocy; it gave a negative reaction, June 26, 1910, a positive one six months later, Jan. 22, 1911, both tests being made by the same serologist. No autopsy was obtained, but the autopsies which have been made on cases of this disease do not mention syphilitic changes in the tissues. Syphilis seems improbable in our case. Noguchi,[1] page 134, alludes to one case of amaurotic family idiocy with a negative reaction.

Case 1 must also be questioned. No definite diagnosis was made. The patient was a 3-year-old child who came in after a three weeks' illness with typhoidal symptoms; Widal reaction, blood culture and Pirquet test were all negative. It was probably a case of miliary tuberculosis.

TABLE 3.—CASES SHOWING POSITIVE SERUM REACTION

Case No.	Age, Years	Sex ..	Admission Diagnosis	Family History	Previous History	Examination	Reaction	Remarks
1	3	M	Miliary Tuberculosis?	Uncle died of phthisis	Always delicate; typhoid symptoms 3 weeks.	Emaciation; glands +; spleen +; T. 98-104 F.; blood culture neg. Widal negative.	Noguchi +	Pirquet negative left in 1 wk; unimproved.
2	12	M	General debility Tb.? 11/14/10	Mother had 3 or 4 miscarriages; 7 other children well.	Developm't backward; dull mentally; pneumonia 4 years ago; scarlet fever 2 years ago; measles 2 years ago.	Poor development; glands +.	Noguchi + 11/26/10	Pirquet + 11/26/10
3	3	M	Tb. Meningitis 4/4/12	Father had "soft chancre" 7 years before; mother had one miscar.; younger brother died one year ago of "heart trouble"; always delicate.	Gen. development normal; present illness began 7 weeks ago.	Typical meningeal signs; Sp. Fl. clear; lymphocytes; Tb. bacilli? Pirquet negat. Double otitis media.	Sp. Fl. Noguchi +++	Died 4/8/12. Autopsy (on head only) showed tb. meningitis, bacilli in exudate at base of brain; no syphilitic changes.
4	1½	F	Broncho-Pneumonia Tb.?	Mother had one miscarriage before birth of patient.	Devel'pm't poor; cough for 3 weeks.	Nutrition poor; color waxy; nasal discharge; nose flat; glands+; bronchitis; consolidation ? tonsils +; spleen +.	+	Pirquet ++

5	7	M	Tb. Hip	Negative	Measles 1 yr. ago; pertussis; date ? Fall 3 wks. ago; R. hip tender since; lame.	Nutrition good; glands +; teeth irreg. and notched; R. hip tender.	Noguchi +	Pirquet negative
6	4	F	Tb. Knee	Negative	Development normal; knee symptoms 3 mos.	Pale, nutrition fair; tonsils +.	Wassermann +	Pirquet ++
7	5	F	Tb. Spine 7/15/10	Negative	Pertussis at 1 year; present trouble began 1½ years ago.	Spinal deformity; glds. +; consolidation R. lung, post. on 1/6/11.	Noguchi + 2/1/11	
8	4	M	Tb. Spine 5/5/11	?	Measles 1 yr. ago and since, pain in back and can not walk.	Pale, nutrition poor. Chest: enlarged bronchial glands ? Abdomen: Tb.? nodules; spleen +; liver +; choked disks (1/20/12, 2/21/12); T. 97-102 F.	Wassermann + 2/24/12	Has had tuberculin regularly since admission to date
9	11	M	Papillitis 1/17/11 Intracranial tumor	Negative	Good till 2 years ago; since, sick headaches.	Nutrition fair; general incoördination; ataxic gait; paralysis of L. abducens; choked disk R.	Noguchi + 2/2/11	Died 2/10/11. Autopsy showed tumor of L. cerebellum. No signs of syphilis anywhere.
10	3	M	Little's disease	?	Always delicate, measles, date ? meningeal symptoms for 2 wks.	Nutrition poor; rigidities; glands +; rickets signs.	Noguchi — 9/5/10 Noguchi + 1/19/11	Pneumonia 1/13/11 Antitoxin.
11	7	F	Microcephalus 1/9/11	Mother had one still-born, one abortion, then the patient and since two still-born.	Backward. Pneumonia at 2 years.	Nutrition poor; physical and mental development backward; tonsils+; head small.	Noguchi + 1/11/11	

TABLE 3.—CONTINUED

Case No.	Age, Years	Sex	Diagnosis Admission	Family History	Previous History	Examination	Reaction	Remarks
12	4	M	Amaurotic family idiocy 6/24/10	Negative	Always delicate; at 1 week vomiting and convulsions.	Emaciation; eyes show characteristic changes; glands +.	Noguchi — 6/26/10 Noguchi + 1/22/11	Death 9/8/11
13	4	F	Epilepsy 2/24/11	Alcoholism, insanity, migraine and cancer in grandparents. Father had "soft chancre" one year before marriage. Mother had 1 child healthy, then miscarriage, then patient.	Measles and pertussis in infancy; diphtheria 2 years ago; characteristic seizures since 7-8 mos. old.	Parietal bosses +; nose flattened; tonsils +; glands +.	Noguchi ++ 2/27/11	
14	8	M	Epilepsy 3/18/11	Epilepsy in maternal G. M. Mother had petit mal? 3 other children well.	Labor instrumental; mentally slow; measles and scarlet fever 4 yrs. ago; varicella 2 mos. ago; pneumonia 3 mos. ago; "spells" for 2 years.	Head asymmetrical; otitis; pigeon-breast.	Noguchi + 3/9/11	
15	10	F	Lesion of spinal cord 9/30/10	Negative	Weak at birth; measles at 7 years; varicella at 9 years; fall 1 yr. ago; since spinal symptoms.	Nutrition poor; paresis R. limbs; teeth notched; glands +; patellar ++; tonsils and adenoids removed; no spirochetes found.	Noguchi + 10/5/10	

16	11	F	Poliomyeloencephalitis	Negative	Pneumonia; date ? Typhoid date ? Unable to walk for 2 yrs.	Teeth notched and decayed; tonsils +; spastic lower limbs.	Noguchi + 2/9/11	
17	3	M	Backward speech 12/17/10	Father had chancre; autopsy showed syphilis. Died 8 mos. ago. Mother's blood shows pos. Noguchi; younger brother has neg. Noguchi. Paternal g. f. had syphilis?	Developm't slow; bronchopneumonia at 2½ years.	Nervous, pale; development poor; can't talk; liver +.	Noguchi + 12/19/10	Pirquet ++
18	½	M	Congenital heart disease 1/4/11	Mother had miscarriage 5 years ago; 3 other child'n healthy; mother died 1 week ago of pneumonia and endocarditis.	Full term, instruments, condition good. Pertussis 3 mos. ago followed by pneumonia. Double otitis, 1 mo.	Nutrition poor; organic heart-signs; ears discharging; weight 10 lbs., 2 oz.	Noguchi + 2/9/11	Left 7/3/11 Mercury from 2/28/11 to 4/6/11
	1¼		10/27/11			Reentered in collapse		Blood and Sp. Fl. from autopsy negative, by both Wassermann and Noguchi. No syphilitic changes in tissues
19	1½	M	Congenital heart disease 11/8/10	Paternal G. F. died of heart trouble; mother had one miscarriage at 7 mos.; 1 other child 2 years old healthy. Mother's blood gives positive Noguchi 12/28/10.	Always delicate.	Developm't and nutrition poor; bronchopneumonia; organic heart murmur; spleen +; liver ++.	Noguchi + 12/1/10	Recovery from pneumonia. Died July, 1911, at home.

TABLE 3.—CONTINUED

Case No.	Age, Years	Sex ..	Admission Diagnosis	Family History	Previous History	Examination	Reaction	Reaction
20	8	M	Endo-pericarditis 3/15/11	Father died phthisis, 2 years ago.	Weak since 5 yrs. old; measles and diphtheria; rheumatism 1 yr. ago; for 1 mo. cough, pain in chest, weakness, dyspnea.	Pale, nutrition fair; tonsils +, glands +. Endopericarditis.	Noguchi Doubtful—3/29/11 Weakly + 4/6/11 Positive 5/11/11	
21	6	F	Endocarditis, mitral aortic? 9/10/11	Father has Noguchi +++ on 3/7/12	Measles; repeated tonsillitis; joint pains recently.	Pale, nutrition poor; glands +, tonsils +; nose flat, teeth bad and irregular; mitral murmurs, aortic murmurs, ?	Wassermann + 2/13/12	Pirquet +++
22	10	F	Endocarditis, mitral aortic? 11/22/10	Mother has goiter; two children died at birth. Mother's blood shows Noguchi ++.	Backward; measles and pertussis at 2 years; mumps at 5 yrs. Tonsillitis at 4 and 7 yrs. Scarlet fever 5 mos. ago, followed by polyartic. rheumatism. Blood and albumin in urine 2 mos. ago.	Nutrition poor; pale; tonsils +; teeth notched; mitral murmurs; aortic murmurs; acute nephritis.	Noguchi + 12/15/10	Died 4/9/11
23	9	M	Endocarditis	Four older children healthy; then 2 miscarriages just before birth of patient. Not preg. since patient.	Development normal; chorea 3 mos. ago; edema for 3 weeks.	Nutrition good; tonsils ++; teeth irregular, notched; mitral murmur; glands +; liver +; no spleen.	Noguchi + (weak)	

24	7	F	Endopericarditis 7/21/11	Mother had 2 miscarriages; poor health since last baby, five years ago.	Measles at 11 mos.; scarlet fever at 4 yrs. Sore throat frequently; for 3 weeks abdominal pain.	Nutrition poor; pale; tonsils +; pericarditis; mitral murmur.	Noguchi + 8/6/11	
25	¼	F	Rhinitis — "snuffles" 1/16/10	Another child died at 5 weeks of a bad "cold."	Normal at birth; "snuffles" for 2 weeks.	Nutrition fair; glands +; bronchitis, nasal discharge; no spirochetes found; spleen +.	Sp. Fl. Noguchi + 4/29/10	Left improved 7/17/10
26	9	M	Tonsils and adenoids	Mother had miscarriages 1½ yr., 4 yrs. and 7 yrs. after birth of twin patients.	Developm't backward; pertussis and mumps at 18 mos.; measles at 5 yrs.; recurrent tonsillitis.	Developm't and nutrition poor; pale; tonsils +; thyroid +; glands +.	Noguchi + 11/9/11 Noguchi + 12/20/11 Noguchi + 2/26/12 Noguchi + 3/23/12	
27	9	M	Tonsils and adenoids	Mother: Noguchi negative. Twin brother of Case 26.	As in brother.	As in brother; thyroid +, etc., but is more vigorous and 2 lbs. heavier. Both received Hg. from 11/9/11 to 3/23/12.	Noguchi + 11/9/11 Noguchi + 12/20/11 Noguchi + 2/26/12 Noguchi — 3/23/12	
28	4	M	Tonsils and adenoids	First 4 pregnancies miscarried at 8 mos.; then 5 living children.	Measles, date ? Varicella, date ? Repeated sore throat; adenoid symptoms.	Developm't poor; pale; tonsils +; nose flat; rachitic signs; albuminuria.	Noguchi + 3/5/12	
29	2	M	Lobar pneumonia	Negative.	Pneumonia at 1 year.	Nutrition poor; pale; nose flat; vacant stare and "grin"; tonsils +.	Wassermann + 2/19/12	Pirquet negative 2/19/12

TABLE 3.—CONTINUED

Case No	Age, Years	Sex ..	Admission Diagnosis	Family History	Previous History	Examination	Reaction	Remarks
30	17*	M	Hare-lip, cleft palate 12/28/10	First child still-born; 3 others living, well; patient is fifth child.	Full term; condition fair.	Condition fair; hare-lip and cleft palate.	Noguchi + Sp. Fluid 1/11/11	Operation 5/22/11 Died 5/23/11
31	1/6	M	Enterocolitis, Convulsions	Negative.	Well at birth; "cold" for 10 days; convulsions for 24 hours.	Emaciation, pallor; moribund. Sp. Fl. neg. for bacteria; Sp. Fl. pos. for Noguchi.	Blood post-mortem gave positive Noguchi	Autopsy 10 hrs. after death; no signs of syphilis.
32	11	F	Fracture of ulna 10/30/10	Mother died insane 5 years ago.	?	Pale; "saddle" nose; teeth irregular, notched; glands +; old scars on both shins. Fracture of L. ulna; *x*-ray shows multiple periostitis in both upper limbs.	Noguchi + 12/6/10	Discharged 1/27/11 Improved on Hg.
33	7	M	Osteomyelitis 3/27/10 Readmitted 12/7/10	Negative	Measles at 1½ years; scarlet fever at 3½ years; for 7 mos. pain in legs, fever, sweating.	Nutrition fair; both tibiæ have discharging sinuses. As above.	Noguchi + 12/20/10	Disch'd 9/10/10 improved Given Hg and KI Improved.
34	1½	F	Anemia	Negative. Father had 2 negative Wassermanns.	Normal development. For 3 weeks daily rise of temperature; cause ?	Pale; nose flat; tonsils +; dactylitis.	Noguchi + 1/7/11 Wassermann — 1/17/11	Calomel. Tests by different men.

*17 days.

35	9	M	Keratitis, tonsils and adenoids 9/13/10	Mother had no miscarriages. Brother Case 36.	Developm't normal till 5 yrs., then pertussis and since deafness and eye trouble. No ear discharge. Mumps at 3 yrs.; varicella at 4 yrs.; scarlet fever 5 mos. ago; diphtheria 5 mos. ago; "Lung-fever" at 2 yrs.; repeated tonsillitis.	Dull. Glands +; tonsils and adenoids; keratitis; deafness; no discharge from ears; nasal discharge.	Noguchi + 9/22/10	
36	8	M	Arthritis and keratitis, 8/14/10 Re-entered 3/12/12	See Case 35 (Brother).	Bronchitis in infancy; tonsillitis often; jaundice 3 mos. ago; joints swollen and tender since.	Developm't and nutrition poor; pale; tonsils and adenoids; glands +; keratitis; knee swollen.	Noguchi positive 9/29/10 after 1 month of Hg. treatment. Wassermann — Noguchi + 3/15/12	Discharged 10/8/10 No treatment since discharge.
37	12	M	Phimosis	Patient oldest child; 3 miscarriages since; 6 other children, well. Twins 2 years ago born with deformed chest. Father had "sores" when first married.	Born at 7 mos., had no finger nails; was asphyxiated; much eye trouble; measles at 6 years; scarlet fever at 8 years; diphtheria 1 year ago.	Development fair; blepharitis; teeth irregular, in double row; palate high; tonsils +; sternum prominent.	Noguchi + 12/18/11	
38	1⅓	M	Rachitis gastro-enteritis 6/29/10	Negative.	Negative	Developm't and nutrition poor; rachitic signs; spleen +.	Noguchi ++ 11/28/10	Pirquet negative. Died 2/11/11. Autopsy showed no gross nor microscopic signs of syphilis.
39	5	F	Still's disease	Negative.	Measles 3 years ago; pertussis 2 years ago; for 1 year pain in limbs and joints; unable to walk.	Nutrition poor; rachitic changes; swelling and stiffness of joints.	Noguchi + 10/24/10 1/9/11 Noguchi — 1/19/11	Hg and KI from Oct. to March, 1911.

TABLE 4.—CASES IN TABLE 2 GROUPED WITH REFERENCE TO THE RELATION OF FAMILY HISTORY, PERSONAL RECORD AND PHYSICAL EXAMINATION TO THE SERUM TEST. POSITIVE CASES

GROUP I

Case No.	Age, Years	Sex ..	Admission Diagnosis	Family History	Previous History	Examination	Reaction	Remarks
13	4	F	Epilepsy 2/24/11	Alcoholism, insanity, migraine and cancer in grandparents. Father had "soft chancre" one year before marriage. Mother had 1 child healthy, then miscarriage, then patient.	Measles and pertussis in infancy; diphtheria 2 years ago; characteristic seizures since 7-8 mos. old.	Parietal bosses +; nose flattened; tonsils +; glands +.	Noguchi ++ 2/27/11	
11	7	F	Microcephalus 1/9/11	Mother had one still-born, one abortion, then the patient and since two still-born.	Backward. Pneumonia at 2 years.	Nutrition poor; physical and mental development backward; tonsils+; head small.	Noguchi + 1/11/11	
17	3	M	Backward speech 12/17/10	Father had chancre; autopsy showed syphilis. Died 8 mos. ago. Mother's blood shows pos. Noguchi; younger brother has neg. Noguchi. Paternal g. f. had syphilis?	Developm't slow; bronchopneumonia at 2½ years.	Nervous, pale; development poor; can't talk; liver +.	Noguchi + 12/19/10	Pirquet ++
26	9	M	Tonsils and adenoids	Mother had miscarriages 1½ yr., 4 yrs. and 7 yrs. after birth of twin patients.	Developm't backward; pertussis and mumps at 18 mos.; measles at 5 yrs.; recurrent tonsillitis.	Developm't and nutrition poor; pale; tonsils +; thyroid +; glands +.	Noguchi + 11/9/11 Noguchi + 12/20/11 Noguchi + 2/26/12 Noguchi + 3/23/12	

27	9	M	Tonsils and adenoids	Mother: Noguchi negative. Twin brother of Case 26.	As in brother.	As in brother; thyroid +, etc., but is more vigorous and 2 lbs. heavier. Both received Hg. from 11/9/11 to 3/23/12.	Noguchi + 11/9/11 Noguchi + 12/20/11 Noguchi + 2/26/12 Noguchi — 3/23/12	
35	9	M	Keratitis, tonsils and adenoids 9/13/10	Mother had no miscarriages. Brother Case 36.	Developm't normal till 5 yrs., then pertussis and since deafness and eye trouble. No ear discharge. Mumps at 3 yrs.; varicella at 4 yrs.; scarlet fever 5 mos. ago; diphtheria 5 mos. ago; "Lung-fever" at 2 yrs.; repeated tonsillitis.	Dull. Glands +; tonsils and adenoids; keratitis; deafness; no discharge from ears; nasal discharge.	Noguchi + 9/22/10	
36	8	M	Arthritis and keratitis, 8/14/10 Re-entered 3/12/12	See Case 35 (Brother).	Bronchitis in infancy; tonsillitis often; jaundice 3 mos. ago; joints swollen and tender since.	Developm't and nutrition poor; pale; tonsils and adenoids; glands +; keratitis; knee swollen.	Noguchi positive 9/29/10 after 1 month of Hg. treatment. Wassermann — Noguchi + 3/15/12	Discharged 10/8/10 No treatment since discharge.
30	17*	M	Hare-lip, cleft palate 12/28/10	First child still-born; 3 others living, well; patient is fifth child.	Full term; condition fair.	Condition fair; hare-lip and cleft palate.	Noguchi + Sp. Fluid 1/11/11	Operation 5/22/11 Died 5/23/11
37	12	M	Phimosis	Patient oldest child; 3 miscarriages since; 6 other children, well. Twins 2 years ago born with deformed chest. Father had "sores" when first married.	Born at 7 mos., had no finger nails; was asphyxiated; much eye trouble; measles at 6 years; scarlet fever at 8 years; diphtheria 1 year ago.	Development fair; blepharitis; teeth irregular, in double row; palate high; tonsils +; sternum prominent.	Noguchi + 12/18/11	

*17 days.

TABLE 4.—CONTINUED

GROUP II

Case No.	Age Years	Sex ..	Admission Diagnosis	Family History	Previous History	Examination	Reaction	Remarks
4	1½	F	Broncho-Pneumonia Tb.?	Mother had one miscarriage before birth of patient.	Devel'pm't poor; cough for 3 weeks.	Nutrition poor; color waxy; nasal discharge; nose flat; glands+; bronchitis; consolidation; tonsils +; spleen +.	+	Pirquet ++
9	11	M	Papillitis 1/17/11 Intracranial tumor	Negative	Good till 2 years ago; since, sick headaches.	Nutrition fair; general incoördination; ataxic gait; paralysis of L. abducens; choked disk R.	Noguchi + 2/2/11	Died 2/10/11. Autopsy showed tumor of L. cerebellum. No signs of syphilis anywhere.
21	6	F	Endocarditis, mitral, aortic? 9/10/11	Father has Noguchi +++ on 3/7/12	Measles; repeated tonsillitis; joint pains recently.	Pale, nutrition poor; glands +, tonsils +; nose flat, teeth bad and irregular; mitral murmurs, aortic murmurs. ?	Wassermann + 2/13/12	Pirquet +++
22	10	F	Endocarditis, mitral, aortic? 11/22/10	Mother has goiter; two children died at birth. Mother's blood shows Noguchi ++.	Backward; measles and pertussis at 2 years; mumps at 5 yrs. Tonsillitis at 4 and 7 yrs. Scarlet fever 5 mos. ago, followed by polyartic. rheumatism. Blood and albumin in urine 2 mos. ago.	Nutrition poor; pale; tonsils +; teeth notched; mitral murmurs; aortic murmurs; acute nephritis.	Noguchi + 12/15/10	Died 4/9/11

23	9	M	Endocarditis	Four older children healthy; then 2 miscarriages just before birth of patient. Not preg. since patient.	Development normal; chorea 3 mos. ago; edema for 3 weeks.	Nutrition good; tonsils ++; teeth irregular, notched; mitral murmur; glands +; liver +; no spleen.	Noguchi + (weak)	
19	1½	M	Congenital heart disease 11/8/10	Paternal G. F. died of heart trouble; mother had one miscarriage at 7 mos.; 1 other child 2 years old healthy. Mother's blood gives positive Noguchi 12/28/10.	Always delicate.	Developm't and nutrition poor; bronchopneumonia; organic heart murmur; spleen +; liver ++.	Noguchi + 12/1/10	Recovery from pneumonia. Died July, 1911, at home.
28	4	M	Tonsils and adenoids	First 4 pregnancies miscarried at 8 mos.; then 5 living children.	Measles, date ? Varicella, date ? Repeated sore throat; adenoid symptoms.	Developm't poor; pale; tonsils +; nose flat; rachitic signs; albuminuria.	Noguchi + 3/5/12	
25	¼	F	Rhinitis — "snuffles" 1/16/10	Another child died at 5 weeks of a bad "cold."	Normal at birth; "snuffles" for 2 weeks.	Nutrition fair; glands +; bronchitis, nasal discharge; no spirochetes found; spleen +.	Sp. Fl. Noguchi + 4/29/10	Left improved 7/17/10
32	11	F	Fracture of ulna 11/30/10	Mother died insane 5 years ago.	?	Pale; "saddle" nose; teeth irregular, notched; glands +; old scars on both shins. Fracture of L. ulna; *x*-ray shows multiple periostitis in both upper limbs.	Noguchi + 11/30/10	Discharged 1/27/11 Improved on Hg.

TABLE 4.—CONTINUED

GROUP III

Case No.	Age, Years	Sex	Admission Diagnosis	Family History	Previous History	Examination	Reaction	Remarks
5	7	M	Tb. Hip	Negative	Measles 1 yr. ago; pertussis; date ? Fall 3 wks. ago; R. hip tender since; lame.	Nutrition good; glands +; teeth irreg. and notched; R. hip tender.	Noguchi +	Pirquet negative
8	4	M	Tb. Spine 5/5/11	?	Measles 1 yr. ago and since, pain in back and can not walk.	Pale, nutrition poor. Chest: enlarged bronchial glands ? Abdomen: Tb.? nodules; spleen +; liver +; choked disks (1/20/12, 2/21/12); T. 97-102 F.	Wassermann + 2/24/12	Has had tuberculin regularly since admission to date
16	11	F	Poliomyeloencephalitis	Negative	Pneumonia; date ? Typhoid date ? Unable to walk for 2 yrs.	Teeth notched and decayed; tonsils +; spastic lower limbs.	Noguchi + 2/9/11	
15	10	F	Lesion of spinal cord 9/30/10	Negative	Weak at birth; measles at 7 years; varicella at 9 years; fall 1 yr. ago; since spinal symptoms.	Nutrition poor; paresis R. limbs; teeth notched; glands +; patellar ++; tonsils and adenoids removed; no spirochetes found.	Noguchi + 10/5/10	
34	1½	F	Anemia	Negative. Father had 2 negative Wassermanns.	Normal development. For 3 weeks daily rise of temperature; cause ?	Pale; nose flat; tonsils +; dactylitis.	Noguchi + 1/7/11 Wassermann — 1/17/11	Calomel. Tests by different men.
29	2	M	Lobar pneumonia	Negative.	Pneumonia at 1 year.	Nutrition poor; pale; nose flat; vacant stare and "grin"; tonsils +.	Wassermann + 2/19/12	Pirquet negative 2/19/12

GROUP IV

3	3	M	Tb. Meningitis 4/4/12	Father had "soft chancre" 7 years before; mother had one miscar.; younger brother died one year ago of "heart trouble"; always delicate.	Gen. development normal; present illness began 7 weeks ago.	Typical meningeal signs; Sp. Fl. clear; lymphocytes; Tb. bacilli? Pirquet negat. Double otitis media.	Sp. Fl. Noguchi +++	Died 4/8/12. Autopsy (on head only) showed tb. meningitis, bacilli in exudate at base of brain; no syphilitic changes.
18	½	M	Congenital heart disease 1/4/11	Mother had miscarriage 5 years ago; 3 other child'n healthy; mother died 1 week ago of pneumonia and endocarditis.	Full term, instruments, condition good. Pertussis 3 mos. ago followed by pneumonia. Double otitis, 1 mo.	Nutrition poor; organic heart-signs; ears discharging; weight 10 lbs., 2 oz.	Noguchi + 2/9/11	Left 7/3/11 Mercury from 2/28/11 to 4/6/11
	1¼		10/27/11			Reentered in collapse		Blood and Sp. Fl. from autopsy negative, by both Wassermann and Noguchi. No syphilitic changes in tissues
24	7	F	Endopericarditis 7/21/11	Mother had 2 miscarriages; poor health since last baby, five years ago.	Measles at 11 mos.; scarlet fever at 4 yrs. Sore throat frequently; for 3 weeks abdominal pain.	Nutrition poor; pale; tonsils +; pericarditis; mitral murmur.	Noguchi + 8/6/11	
14	8	M	Epilepsy 3/18/11	Epilepsy in maternal G. M. Mother had petit mal? 3 other children well.	Labor instrumental; mentally slow; measles and scarlet fever 4 yrs. ago; varicella 2 mos. ago; pneumonia 3 mos. ago; "spells" for 2 years.	Head asymmetrical; otitis; pigeon-breast.	Noguchi + 3/9/11	
2	12	M	General debility Tb.? 11/14/10	Mother had 3 or 4 miscarriages; 7 other children well.	Developm't backward; dull mentally; pneumonia 4 years ago; scarlet fever 2 years ago; measles 2 years ago.	Poor development; glands +.	Noguchi + 11/26/10	Pirquet + 11/26/10

TABLE 4.—CONTINUED

GROUP V

Case No.	Age, Years	Sex ..	Admission Diagnosis	Family History	Previous History	Examination	Reaction	Remarks
1	3	M	Miliary Tuberculosis?	Uncle died of phthisis	Always delicate; typhoid symptoms 3 weeks.	Emaciation; glands +; spleen +; T. 98-104 F.; blood culture neg. Widal negative.	Noguchi +	Pirquet negative left in 1 wk; unimproved.
7	5	F	Tb. Spine 7/15/10	Negative	Pertussis at 1 year; present trouble began 1½ years ago.	Spinal deformity; glds. +; consolidation R. lung, post. on 1/6/11.	Noguchi + 2/1/11	
6	4	F	Tb. Knee	Negative	Development normal; knee symptoms 3 mos.	Pale, nutrition fair; tonsils +.	Wassermann +	Pirquet ++
20	8	M	Endo-pericarditis 3/15/11	Father died phthisis, 2 years ago.	Weak since 5 yrs. old; measles and diphtheria; rheumatism 1 yr. ago; for 1 mo. cough, pain in chest, weakness, dyspnea.	Pale, nutrition fair; tonsils +, glands +. Endopericarditis.	Noguchi Doubtful—3/29/11 Weakly + 4/6/11 Positive 5/11/11	
12	4	M	Amaurotic family idiocy 6/24/10	Negative	Always delicate; at 1 week vomiting and convulsions.	Emaciation; eyes show characteristic changes; glands +.	Noguchi — 6/26/10 Noguchi + 1/22/11	Death 9/8/11
10	3	M	Little's disease	?	Always delicate, measles, date ? meningeal symptoms for 2 wks.	Nutrition poor; rigidities; glands +; rickets signs.	Noguchi — 9/5/10 Noguchi + 1/19/11	Pneumonia 1/13/11. Antitoxin.

31	1/6	M	Enterocolitis, Convulsions	Negative.	Well at birth; "cold" for 10 days; convulsions for 24 hours.	Emaciation, pallor; moribund. Sp. Fl. neg. for bacteria; Sp. Fl. pos. for Noguchi.	Blood post-mortem gave positive Noguchi	Autopsy 10 hrs. after death; no signs of syphilis.
38	1⅓	M	Rachitis, gastro-enteritis 6/29/10	Negative.	Negative	Developm't and nutrition poor; rachitic signs; spleen +.	Noguchi ++ 11/28/10	Pirquet negative. Died 2/11/11. Autopsy showed no gross nor microscopic signs of syphilis.
33	7	M	Osteomyelitis 3/27/10 Readmitted 12/7/10	Negative	Measles at 1½ years; scarlet fever at 3½ years; for 7 mos. pain in legs, fever, sweating.	Nutrition fair; both tibiæ have discharging sinuses. As above.	Noguchi + 12/20/10	Disch'd 9/10/10 improved Given Hg. and KI. Improved.
39	5	F	Still's disease	Negative.	Measles 3 years ago; pertussis 2 years ago; for 1 year pain in limbs and joints; unable to walk.	Nutrition poor; rachitic changes; swelling and stiffness of joints.	Noguchi + 10/24/10 1/9/11 Noguchi — 1/19/11	Hg. and KI. from Oct. to March, 1911.

The patient was taken out of the hospital after a week's stay and nothing further was heard of him. There was nothing about him to suggest syphilis.

Concerning the other cases of the group, there is possibly more ground for considering them as syphilitic; five of them involve disease of the osseous system: two of joint trouble thought to be tuberculous, a chronic osteomyelitis, a case of Still's disease, one of Little's disease with bony changes thought to be rachitic. The tendency of the syphilitic virus to attack the bony tissues is well known, and syphilis cannot with certainty be excluded in any of these cases. Clinical observations and serum tests of the future must determine how frequently these bone affections are due to luetic infection.

The case of endocarditis included in this group is interesting; it showed a reaction at first "doubtful," a week later "faintly positive," and a month later "positive"; in view of these reactions and of the frequency with which the other cases of endocarditis of this series, cases with suggestive or characteristic signs of syphilis, have shown positive reactions, there is probably little doubt of the basic nature of this case, little doubt that it is syphilis. But as the case illustrates a condition "on trial," as it were, in this paper, and presented none of the signs regarded in the past as suggestive of syphilis, it must be classified, for the present, at least, in this group. Studies of the future may or may not show that endocardial affections are of such frequent occurrence in congenital syphilis that their presence is suggestive of the disease and must always arouse a suspicion of its existence.

The third supposition, that the reaction is incorrect and is due to some error in technic, must be considered. Such an error might arise from (1) change in the blood after taking and before testing, or from (2) some imperfection in one of the substances or reagents used. Due care was used in the handling of the blood, keeping it at a proper temperature, etc. It is of course possible that hemolysis may have taken place before testing and thus at the test hemolysis was prevented and a positive reaction obtained. But against this theory is the fact that specimens of blood from other patients at the hospital, obtained at the same time and handled in the same manner, gave in some instances negative reactions, in others positive reactions. Similarly with the various substances used for antigens, amboceptors, etc.; the same materials used in our cases were used at the same time on patients from another hospital and found to be working well, giving positive reactions on known syphilitics, mostly adults, yet negative results on still others undoubtedly not syphilitic. I have taken pains to "check up" with Dr. Nicoll these points by review of the original records on the given dates of each of the cases in Group V. and it is evident that the error, if error there be, is not in the quality of the different substances used. I cannot be so sure of the absence of error

under the first possibility, i. e., some change in the blood used; particularly might this be true with regard to Case 31, when the blood was obtained at autopsy ten hours after death; for Candler and Mann have shown that post-mortem decomposition may alter the reaction whether of the blood or spinal fluid, an ante-mortem positive reaction being converted into a negative, and vice versa.

Taken as a whole, then, Group V may be summarized briefly as follows: There is no ground, except a positive serum reaction, for regarding four of the group, Numbers 1, 12, 20 and 31, as cases of syphilis; there is some ground for regarding the remaining cases as syphilitic, and in them this disease cannot with certainty be excluded. Our third question, then, Does a positive serum reaction, without suggestive physical signs, mean syphilis? must, in the present state of our knowledge, be answered in the negative. Investigations of the future, however, may broaden our conception of the term "suggestive" signs so that it will include signs now not regarded as "suggestive."

NEGATIVE CASES

The negative cases require but little further comment. The diagnoses are given in Table 1. The relative frequency of suggestive family history and suggestive physical examination in the two divisions, positive and negative, has already been noted, there being far fewer such records in the negative than in the positive cases. Among the negative ones were only three cases with such marked physical signs that syphilis could not be excluded. The first of these was a 2-months-old baby, of the Mongolian type of idiocy, with a congenital heart lesion, asymmetrical head, flattened nose and "chicken breast." He was the fifth child, the first four pregnancies having resulted in miscarriages. The test (Noguchi) was done with his spinal fluid; possibly his blood would have given a positive result.

The second suspicious, yet negative, case was a younger brother of patient, Case 17. He was much below par, with bony changes regarded as rachitic, and with a well-marked syphilitic family history (Table 3, Case 17).

The third case was a 12-year-old girl, of backward development, with marked keratitis and suspicious looking teeth.

RÉSUMÉ

Surveying now as a whole this series of 101 hospital children who have been tested by the Wassermann serum reaction, certain facts strike us.

First, we are impressed with the large number of cases presenting a positive reaction, 38 per cent., over a third, giving such a result. The most of these, as we have seen, we are justified in regarding as syphilis; all, in fact, except the patients in Group V. Deducting the ten cases

forming this group, we have twenty-nine (28 per cent.) cases of syphilis among the first hundred children, selected mostly at random, in one of our large American hospitals; that is, nearly one out of every three patients. It has been difficult in the past to obtain an accurate idea of the prevalence of congenital syphilis. That syphilis in general is a lamentably wide-spread disease is well known. Erb, for example, found that out of 10,000 cases of all varieties of disease in his practice, 21 per cent. had syphilis. He believes that 12 per cent. of the adult population of Berlin has syphilis. This means, eventually, a large amount of the congenital form of the disease. Yet it is not generally regarded as being common. Beekel, for example, examined the record of the Babies' Dispensary in Cleveland and found only forty-five cases among 3,500 patients, about 1.33 per cent.; these were all clinical cases and before the days of the serum test.

The observations made in this paper, based on clinical examination and the serum test, would tend to show, however, that there is a large amount of congenital syphilis among hospital patients.

Next we are struck with the great variety of conditions in which we find a positive serum reaction, corresponding with the protean character of syphilis. The greatest number of positive reactions is found, furthermore, in the bony, nervous and circulatory systems, tissues, it will be recalled, particularly apt to be attacked by the syphilitic virus.

The comparatively large number of positive cases without physical signs, the "symptomless" children, is another striking phenomenon, fourteen of the cases (37 per cent.) being so lacking. This again is quite in keeping with the character of congenital syphilis, at least of the late variety, and emphasizes the difficulty of arriving at a diagnosis, and the importance of the serum test in unearthing these obscure cases.

The number of cases reported in this series is, however, small, and it may be that analysis of larger numbers of cases will modify the points which have been discussed, and that the figures obtained in the first hundred cases may be considerably altered by future studies. Enough has been set forth, however, to demonstrate the importance of the serum test in studying our anemic, maldeveloped children and the desirability of applying this test on a large scale to these children, in order, first, to determine to what extent syphilis prevails among them, and, secondly, to institute proper treatment.

The subject is, to my mind, an important one, a broad one; important not only to the victims of the disease itself, but also to the community at large and for the future welfare of the race. If congenital syphilis is nearly as prevalent among certain classes of the community as the studies in this paper would seem to indicate, it is a matter of grave concern to all, especially to us as pediatricians, on whom must devolve the responsibility of determining the extent of the evil and its proper management. We

have had put into our hands recently, in the Wassermann serum test, a method of investigation which, together with careful, painstaking clinical observations on a large scale, will give us accurate information, as never before, concerning a malady notoriously fatal in extreme infancy, lamentably blighting in later childhood. But the use of this new weapon must be wide-spread, must be carried out in large numbers of patients before we can answer finally the questions propounded in this paper and the various points suggested by those questions.

This study is therefore offered, not by any means as a final solution of the questions, but rather as a preliminary report, and with the hope that others will also take up and carry on the work.

I am indebted to my fellow members of the Hospital staff for permission to study the children in their wards. I am also greatly indebted to Drs. E. R. LeCount and J. H. Hewitt for the reports on the autopsies.

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ACUTE DUODENAL INDIGESTION IN CHILDREN*

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The relation between the physiology of digestion and the diseases of the gastro-intestinal canal has received considerable attention in recent years and has thrown much light on many obscure digestive disturbances. A large part of our knowledge about bile and the effects of obstruction to the flow of the bile, comes from animal experiments and there is only a relatively small amount of literature on the physiology and pathology of bile which has been applied to infancy and childhood. A résumé of these facts is necessary because they explain much that, otherwise, is obscure in the treatment of acute duodenal indigestion, and give a physiologic foundation for our conception of the pathologic processes to be studied. They naturally divide themselves into physiology of bile, biochemistry of bile and its products of decomposition, and the action of bile during digestion.

PHYSIOLOGY

Bile varies not only in amount, but also as regards its composition, as is shown by the accompanying table.[1]

TABLE SHOWING COMPOSITION OF BILE FROM THE LIVER AND FROM THE GALL-BLADDER

	Liver-Bile	From Gall-Bladder
Solids	2.06	16.02
Water	97.94	83.98
Mucin and pigments	0.28	4.44
Alkali bile-salts	0.85	8.72
Taurocholates	0.11	1.93
Glycocholates	0.74	6.79
Fatty acids from soaps	....	1.06
Cholesterol	0.08	0.87
Lecithin	....	0.14
Fats	0.03	0.15
Soluble salts	0.80	0.30
Insoluble salts	0.02	0.24

Bile pigments and salts find their way into the intestine very early in the third month of fetal life.[2] This bile, together with the secretion

*Obstructive jaundice, the terminology used in this paper, is that adopted by the Department of Pediatrics of the Harvard Medical School.

*From the Children's Medical Department, Massachusetts General Hospital.

1. Hammarsten, Olaf: Nova acta Reg. Soc. Upsal, Serie III, 1894; quoted in Abderhalden-Hall: Text-book of Physiological Chemistry, New York, 1908, p. 517.

18. The attempt was also made to determine whether the patient's blood condon, 1904, p. 319.

of the rest of the canal and some desquamated epithelium, accumulates to form the meconium. After birth the cycle of a normal digestion starts and from then on is elaborated until it reaches the adult type of digestion. The intestinal canal is sterile at birth, but shortly afterwards it becomes infected and remains so for the rest of life. The type of bacteria inhabiting the canal depends on the kind of food which surrounds them. They tend to belong to the acid-forming group while the baby is fed with human milk, and to the putrefactive- or alkali-forming group when the food is cow's milk.[3] This fact has a bearing on the chemical changes which bile undergoes after it enters the intestinal canal. Bile is excreted from the liver in the form of bilirubin and is changed through oxidation and bacterial action into biliverdin and later hydrobilirubin. This in its turn may be converted into leukohydrobilirubin, when decomposition is more intense. A considerable part of the bile which has already performed its part in digestion is absorbed and carried back to the liver to be reconverted into bilirubin. Hydrobilirubin does not appear in appreciable amounts in the feces until putrefaction is well established. This commences when a baby begins to take cow's milk, which contains larger quantities of casein than human milk and thus gives a suitable food for the proteolytes, or putrefactive group of bacteria, to grow on. There are two bodies, urobilin and urobilinogen, which correspond with hydrobilirubin and leukohydrobilirubin but which are not chemically identical with these bodies. It has been proved that urobilinogen cannot be formed without the action of bacteria and so it is impossible to obtain Ehrlich's "aldehyde" test for urobilinogen in either the urine or the feces when bile is blocked from the intestines. This body is of enough importance in the consideration of acute duodenal indigestion to warrant a detailed description of it.

UROBILINOGEN

In 1901 Ehrlich[4] observed that an acid solution of dimethylaminobenzaldehyd caused a cherry-red color to appear in urine, which became much more intense in many pathologic conditions. There was considerable discussion about the significance of this reaction until O. Neubauer[5] established the fact that it is a test for urobilinogen. It is easily oxidized into urobilin when exposed to air and light.[6]

3. Kendall: Observations on Aciduric Bacteria, Jour. Med. Research, 1910, N. S., xvii, 153.

4. Ehrlich: Ueber die Dimethylamidobenzaldehydreaction, Med. Wchnschr., Berl., 1901, ii, 151.

5. Neubauer: Ueber die neue Ehrlichsche Reaction mit Dimethylaminobenzaldehyd. Sitzungsbericht der Gesellsch. f. Morph. u. Phys. in München, 1903. Reported in München. med. Wchnschr., 1903, 1, No. 2, p. 1846.

6. Saillet: De L'Urobiline dans les urines normales, Rev. de méd., 1897, xvii, 109.

Bookman[7] and Langstein[8] summarize the knowledge of the subject and incidentally mention results which correspond with my observations on its action during occlusion of the bile ducts. The decomposition of bile takes place mostly in the large intestine where bacterial action is most pronounced. Herter[9] showed that Ehrlich's "aldehyde" reaction could be augmented by skatol and also intensified by a diet rich in meat. He was also able to cause the reaction to disappear from the urine of dogs when he gave them a milk instead of a meat diet. This latter observation was probably due to the change in bacterial action and a lessened decomposition, because I have found the reaction repeatedly in the urine of babies fed on mixtures of cow's milk only. Urobilinogen is only present in the urine when bile flows into the intestinal canal and is always absent when there is occlusion of bile. The test is performed in the following way:

Add a few drops of Ehrlich's reagent (2 per cent dimethylaminobenzaldehyd in 5 per cent. HCl) to 5 c.c. of unheated urine. There is no change of color. Then gently warm the urine and if urobilinogen is present in normal amounts it will turn a delicate cherry-red color. This can be best seen by looking down through the depth of the test tube. If urobilinogen is present in abnormal amounts, the urine turns distinctly cherry-red on adding the reagent in the cold. When urobilinogen is absent, the cherry-red color cannot be obtained even after heat is applied.

THE RELATION OF BILE TO THE DIGESTION AND ABSORPTION OF FAT

Bile has the property of activating the pancreatic proferment steapsinogen into steapsin.[10] The absence of bile, however, does not stop the action of steapsin when it is once secreted; without it the fats may be split in part, but they are imperfectly absorbed.[11] The action of bile on fat during digestion is not simple and the changes which fat undergoes must be briefly enumerated before it can be discussed. The greater portion of the fat in cow's milk is in the form of neutral fat. During digestion neutral fat is first split into fatty acids, which in turn are

7. Bookman: Die physiologische Bedeutung und der klinische Wert der Ehrlichschen Dimethylaminobenzaldehyd reaktion im Kindesalter. Jahrb. f. Kinderh. N. F., 1906, lxiv, 206.

8. Langstein: Ein Beitrag zur Kenntnis des weissen Säuglingsstuhls, Festschrift für Salkowski.

9. Herter: Ehrlich's Aldehyd Reaction in the Urine. Jour. Biol. Chem., 1908, iv, 403.

10. Nencki: Ueber die Spaltung der Säureester der Fettreihe und der aromatischen Verbindungen im organismus durch das Pancreas. Arch. f. exper. Path. u. Pharm., 1886, xx, 367.

11. Schwann: Versuche um auszumitteln ob die Galle im Organismus einer für das Leben wesentliche Rolle spielt. Müller's Arch. f. Anat. Physiol. u. wissensch. Med., 1844, 127; Dastre: Recherches sur la bile. Arch. phys. norm. et path. 1890, 5 S., ii, 315.

converted into soaps. Pflüger's[12] investigations led him to the conclusion that unsplit fat cannot be absorbed. There is much evidence which warrants the statement that the stage of soap formation is necessary for the most efficient absorption of fat.[13] The emulsification of fats is favored by the presence of bile, which also increases the fat-splitting action of the pancreatic juices eight times or more.[14] It has been proved that the cholic acid component of the bile salts is responsible for the rapid digestion of fats.[15] Bile has the property of dissolving fatty acids,[16] of increasing the solubility of soaps in water, and of preventing the gelatinization of soaps.[17] Its action on soaps is probably of more importance than its action on fatty acids. When bile is occluded from the intestinal canal, absorption of fat is interfered with and metabolism is abnormal.

THE EFFECT OF OBSTRUCTION OF BILE ON THE METABOLISM

Most of the knowledge on this subject comes from animal experiments, but there are a few experiments on man. Fr. Müller's[18] and Riecke's[19] experiments on adults with occlusion of the bile ducts, showed that there was no abnormal loss of nitrogen, while R. Schmidt[20] found an enormous loss of nitrogen in a patient with catarrhal jaundice plus anorexia, who was very much underfed. The conclusion may be drawn from these experiments that there is no loss of nitrogen during the disease unless anorexia becomes pronounced and is accompanied by starvation. The digestion of carbohydrates also progresses in a normal manner. Experimentally, the absorption of fat is seriously interfered with; only 40 per cent. of the fat ingested is absorbed instead of the normal 90 per cent. Rohmann[21] and Fr. Müller[18] have shown that the same relation holds good in man. In obstruction to bile, the fat content

12. Pflüger's Arch. f. d. ges. Physiol., 1900, lxxx, 111; 1900, lxxxi, 385; 1900, lxxxii, 303; 1901, lxxxv, 1; 1901, lxxxviii, 299; 1902, lxxxix, 281; 1902, xc, 1.

13. Talbot: See review of literature in Physiology and Pathology of the Digestion of Fat in Infancy. Am. Jour. Dis. Child., 1911, i, 173.

14. Hewlett: Effect of Bile upon the Ester-Splitting Action of Pancreatic Juice. Bull. Johns Hopkins Hosp., 1905, xvi, 20.

15. Fürth and Schutz: Ueber die Bedeutung der Gallensäure für die Fettverdauung. Zentralbl. f. Physiol., 1906, xx, 47.

16. Moore and Rockwood: On the Mode of Absorption of Fats. Jour. Physiol., 1897, xxi, 58.

17. Moore, Rockwood and Parker, quoted from von Noorden, Metabolism and Practical Medicine, Chicago, 1907, ii.

18. Müller: Untersuchungen über Ikterus. Ztschr. f. klin. Med., 1887, xii, 45.

19. Riecke: Harnstoff, Ammon, u. Phosphorsäuregehalt Leberkranker. Diss. Wurzburg, 1886; quoted from von Noorden, Metabolism and Practical Medicine, Chicago, 1907, ii, 236.

20. Schmidt: Zur Stoffwechselpath. des Ikterus catarrhalis u. zur Frage der Paracholie. Zentralbl. f. inn. Med., 1898, xix, 113.

21. Rohmann: Beobachtungen an Hunden mit Gallenfistel. Pflüger's Arch. f. d. ges. Physiol., 1882, xxix, 509.

of the feces is more than double the normal, while 55 per cent. of the fat in the food, instead of 8 to 12 per cent. as in health, is lost in the feces. Schmidt[22] found in adults that 21.45 per cent. to 26.61 per cent. of the dried feces of healthy individuals is fat and that this fat represented 5.16 per cent. to 5.91 per cent. of the fat ingested. In closure of the bile duct he found that 43.87 per cent. to 53.59 per cent. of the dried feces was fat and that 22.79 per cent. to 27.70 per cent. of the fat ingested was lost in the feces. Gaultier[23] found an absorption of only 37 per cent. to 53 per cent. of the fat in the food. These estimations of fat in the stool were not done by the newer method of Kumagawa and Suto,[24] which might have shown larger losses of fat, as it gives higher figures than the older methods. The clay color of the stools is caused partly by the absence of bile pigments and partly by the presence of excessive quantities of fat. It must be remembered, in this connection, that leukohydrobilirubin is white bile and that the white stools, such as are seen in other types of indigestion due to fat, do not mean of themselves that there is no bile in the feces.

Bile has no effect on the digestion of sugar, but it has been known for a long time that sugars have an unfavorable influence on patients with acute duodenal indigestion. A possible explanation of this fact is that excessive amounts of sugar may supply a media of growth for the normal fermentative bacteria of the upper gastro-intestinal canal. These bacteria may overgrow in suitable surroundings to such an extent that as a result of their activities a secondary irritation of the duodenal mucosa is set up. This theory is based on the assumption that bacteria of the fermentative group are present to act on the sugar. Starch, on the other hand, is broken down slowly into sugars so that only a small amount of sugar is set free at a time. Thus, in the first instance, a flood of sugar stimulates the bacteria to intense activity, while in the second, there is only a dribble which is absorbed before it can effect the bacteria.

Acute duodenal indigestion is a relatively common disease. During the past year there have been twenty-four cases in the Children's Medical Out-Patient Department of the Massachusetts General Hospital, which I was able to study with more or less care. The onset of the disease varies; it may be sudden with fever, vomiting, pain in the stomach which

22. Schmidt: Schmidt and Strasburger. Die Fäzes des Menschen. 3 Aufl. Berlin, 1910, 153.

23. Gaultier: Essai de coprologie clinique de l'exploration fonctionelle de l'intestin par l'analyse qualitative des graisses dans les feces. Presse méd., 1904, xii, 612.

24. Kumagawa and Suto: Ein neues Verfahren zur quantitativen Bestimmung des Fettes und der unverseifbaren Substanzen im tierischen Material nebst der Kritik einiger gebräuchlichen Methoden. Biochem. Ztschr., 1908, viii, 212.

lasts one or two days and is followed by jaundice, clay colored movements, bile in the urine and loss of appetite; or insidious, without fever, following some indiscretion in diet, more especially fats or sugars. Stooss[25] reports a family of children in which jaundice was brought on by a honey cure prescribed by the father. Large and small epidemics of jaundice have been reported.[26] Apparent contagion was traced from one sister to the other in two of my cases. These cases of infectious jaundice were clinically identical with most of the cases studied by me, but did not run the severe course described in Weil's disease. All but two of seventy cases which were seen in the out-patient department of the Massachusetts General Hospital since 1903 occurred between the first of September and the middle of January.

CASE REPORT

The following case illustrates the various points brought out in the discussion of the disease:

Herbert C. (M.G.H., O.P.D. 166,473) was first seen Feb. 20, 1911. He was 10 years old. His family history and past history were unimportant. He was well up to six weeks previously, when he complained that his stomach was hurting him. At the time he was eating ten to twelve raw apples a day. About two weeks ago he became feverish, and complained of headache; seven to eight days ago he became quite yellow and the fever disappeared. He noticed that his stomach was swollen but did not see that his urine and stools were abnormal until five days ago when the jaundice became more marked and the family physician was called in. The stools on examination were found to be lead- to clay-colored and the urine was very dark.

The physical examination showed very marked icterus of skin, soft palate and conjunctivæ. The pupils were equal and reacted to light. The mouth, throat, heart, lungs and abdomen were normal. The liver dulness extended from the upper border of the fourth rib to 4 cm. below the edge of the ribs in the nipple line, where the edge was easily felt; it was not tender. The spleen was not palpable. The urine contained large quantities of bile and showed no test for urobilinogen. This meant that there was no bile flowing into the digestive tract.

Treatment consisted in restricting his diet to meats, starches and skimmed milk, fats and sugars being excluded as far as possible. Three days later, February 23, he was again seen and reported that he was much better. The jaundice was less marked and although the urine still contained bile (bilirubin), it also showed a large excess of urobilinogen. This meant that bile was entering the intestinal canal. The stool was gray, formed, shiny, of foul odor; it showed under the microscope no meat fibers or starch granules, but there was a large excess of fat in the form of soaps.[27] Four days later, February 27, he reported that he was getting along splendidly, that the urine was of more normal color, and that the day previous the stool looked more natural. The urine contained less bile (tincture of iodin test) and still had an excess of urobilinogen. The stool was

25. Stooss: Pfaundler and Schlossmann: Diseases of Children. Philadelphia and London, 1908, iii, 269.

26. Stooss: *Loc. cit.*, note 25; Vaisey: An Epidemic of Infectious Jaundice. Brit. Med. Jour., 1911, i, 935; Hallowes: An Epidemic of Infectious Jaundice. Brit. Med. Jour., 1911, i, 1464.

27. The methods used in examining the stools were reported by me in Arch. Pediat., February, 1911.

light yellow, smooth and macroscopically perfectly digested. Under the microscope it showed a small excess of fat in the form of soaps. The flow of bile into the intestinal canal was therefore nearly normal. On March 3 he reported that the stools were brown and constipated and the urine almost normal. On examination he was very slightly jaundiced, the liver had diminished in size, extended from the sixth rib to just below the costal margin in the nipple line. He looked better in every way and had gained 5 pounds in twelve days on the restricted diet. The urine showed a slightest possible trace of bile by the iodin test and a large excess of urobilinogen. The stool was still light yellow, smooth and of foul odor. Under the microscope it showed a small amount of fat in the form of soaps.

The analysis of the cases studied brought out several interesting facts: The disease came as a complication of such infections as otitis media, diphtheria, and the exanthemata in 15 per cent. of the cases. The onset was sudden with fever and vomiting in 75 per cent., and therefore suggested an infectious origin; the liver was enlarged in 74 per cent., and tender in 13 per cent.; the spleen was not felt in any case. Urobilinogen was absent from the urine in every case where there was complete obstruction to bile and was found in excessive amounts when the obstruction was removed. The stools were recorded as white in 36 per cent., creamy in 14 per cent., and clay colored in 50 per cent. of the cases during obstruction, and, under the microscope, always showed an excess of fat which was entirely in the form of soaps, while there was constipation, and as both fatty acids and soaps when there was diarrhea. In one instance in which the diet was particularly bad, there was also an excess of starch, but in all other cases starch and meat were perfectly digested.

When there is complete obstruction to the common duct, bile in the form of bilirubin is dammed back into the circulation, colors the tissues and part overflows in the urine. Urobilinogen cannot be found in the urine because bacterial action on bile is necessary for its formation; this of course only takes place in the intestinal canal. As a result, the fat in the food is digested and absorbed only in part, and there is a clay-colored alcoholic stool which is composed almost entirely of fat. In the majority of my cases this fat was in the form of soaps. In some instances there is constipation and in others a diarrhea of putrid, rancid stools containing fine mucus. The diarrhea is a result of prolonged irritation of the intestinal mucous membrane, due to the stagnation and decomposition of fat, which is brought about by the action of the intestinal juices and bacteria, thus complicating the duodenal indigestion with a secondary intestinal indigestion. When the bile flows again into the intestine the fat quickly disappears from the stool and abnormal quantities of urobilinogen appear in the urine. On the basis of these findings two explanations may be given: Either the excessive amounts of urobilinogen are due to excessive putrefaction accompanying the disease,

plus a diet containing a large amount of meat, or acute duodenal indigestion is not a simple blocking of the common duct by mucus. It is conceivable that the agent which caused the plug of mucus to form in the common duct may have extended up into the small bile capillaries of the liver. In that case, the liver cells could not act normally and urobilinogen would not be converted back into bilirubin in the normal manner; this would result in an obstruction in the liver, which would cause urobilinogen to back up and overflow in excessive amounts in the urine. Münzer and Block[28] conclude as a result of their experiments that increased amounts of urobilinogen in the urine always means disease of the liver cells to a greater or less degree.

TREATMENT

Metabolism experiments and an understanding of the physiology of bile makes it obvious that fat and sugars should be excluded from the diet. Conversely proteins, especially meat, fat-free milk, or skimmed milk, and thoroughly cooked simple starches (potato is the least digestible) may be safely given. Fortunately, the disease is of relatively short duration, because a fat-free diet could not supply the requisite number of calories to sustain health indefinitely. The appetite is always poor and can be best stimulated by tincture of nux vomica, in doses corresponding to the age of the patient. Mucus is the natural protective agent of the gastro-intestinal canal and is thrown out by the mucous membrane whenever there is any form of irritant present. We know that mucus is soluble in alkalies and precipitated by acids, therefore, the mucus plug in the bile duct may be best reached by large doses of alkalies (for example bicarbonate of soda).

The prognosis is always good for life, but recurrences are not infrequent; our knowledge of the pathologic anatomy is, therefore, very scanty. Much work must be done by the pathologist before we can know whether acute duodenal indigestion is a purely local disease or one in which the liver tissue itself is involved.

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28. Münzer and Block: Ueber den Nachweis des Urobilinogens und des Urobilins und die klinische Bedeutung dieser Körper. Arch. f. Verdauungsk., 1911, xvii, 260.

RÉSUMÉ ON INFECTIOUS DISEASES

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ANIMAL EXPERIMENTATION IN SCARLET FEVER

During the past year animal experimentation in scarlet fever has brought out certain facts which may lead us to a solid etiologic basis. Bernhardt[1] reports some interesting experimental work on the transmission of scarlet fever to various forms of monkeys (*Macacus rhesus, Macacus cynomolgus, Cercopithecus griseus fulginosis*). The coating was removed from the tongue of a child in the early stages of the disease before the appearance of the so-called "strawberry tongue," and mixed thoroughly with normal salt solution by shaking for an hour. He injected subcutaneously 4 c.c. of this emulsion into the groin of a monkey, and part he rubbed into the mucous membrane of the mouth, tongue and tonsils. After a few days there was a rise of temperature and swelling of the inguinal glands, and on the fifth day the animal showed well-marked symptoms similar to those seen in man, namely, an erythematous exanthem, elevation of temperature, swollen lymph-nodes and scarlatinal tongue. The swollen nodes were removed and treated in the same manner as the coating from the tongue, and the emulsion was injected into another monkey. In this manner he was able to transmit the disease through three different monkeys; but the fourth showed no reaction.

In some of the lymph-nodes streptococci were present, while in others they could not be found. The presence or absence of streptococci did not affect the experiments in the slightest degree. The material injected was sterile in cultures and produced no disturbances when injected into mice.

Control inoculations with streptococci caused no reactions.

Bernhardt concludes that there is a virus present in the coating of the tongue, in the lymph vessels of the skin and in the lymph-nodes. This virus will produce in monkeys certain symptoms which are practically identical with those of scarlet fever in man. That the virus is filterable he proved by obtaining the scarlatinal symptoms in two cases with material that was previously passed through a bacteria filter.

Landsteiner, Levaditi and Prasek,[2] working along the same line as Bernhardt, transmitted a similar chain of scarlet fever symptoms to chimpanzees. With the lower forms of monkeys used by Bernhardt they were not successful.

1. Bernhardt: Deutsch. med. Wchnschr., April 27, 1911, p. 791.
2. Landsteiner, Levaditi and Prasek: Ann. de l'Inst. Pasteur, October, 1911. p. 754.

The symptoms in chimpanzees were similar to those in man, and a necropsy on one of them showed skin and kidney lucsions resembling those found in human beings. Subcutaneous injections of streptococci isolated from one of their cases caused only a local abscess, while an intravenous injection produced no symptoms whatsoever.

Their research corroborates the conclusion of Bernhardt that the virus is filterable, and that the streptococci play at the most a secondary part.

BACTERIOLOGY OF SCARLET FEVER

Streptococcus.—Schleissner[3] reports the results of extensive investigation in 108 cases of scarlet fever, with special reference to the presence and rôle of the streptococcus. In sixty of the cases (55 per cent.) the streptococcus was found in the blood culture, while in forty-eight cases it was absent in spite of repeated examinations. He found no connection between a positive blood culture and the prognosis; 31 per cent. of the children showing the streptococcus and 35 per cent. of those not showing it had complications. The presence of the streptococcus did not appear to affect the temperature curve. Notwithstanding these negative results Schleissner believes that the streptococcus plays more than a secondary rôle.

Bacillus.—Vipond[4] isolated from the lymph-nodes of seven typical cases of scarlet fever a large bacillus with rounded ends, which he considers specific for the disease. It grows readily on the ordinary culture media, and on injection into monkeys produces symptoms similar to those obtained by Bernhardt with his filterable virus from the lymph-nodes of monkeys.

Koessler and Koessler,[5] after numerous serum experiments, conclude that (1) the serum of scarlet fever patients contains specific antibodies for an unknown virus; (2) this unknown virus is present especially in the cervical lymph-nodes.

HYPEREMIA TEST IN SCARLET FEVER

Leede[6] reports the results of his observations concerning the diagnostic test for scarlet fever originated by Rumpel in 1909. Passive hyperemia is produced by a broad rubber constrictor placed on the arm above the elbow joint, care being taken not to obstruct the arterial flow. After ten or fifteen minutes the band is loosened. The skin over the flexor surface of the elbow joint is then stretched until it appears anemic, and if the reaction is positive, petechiæ are readily visible. Leede attributes the phenomenon to changes in the walls of the capillaries.

3. Schleissner: Ztschr. f. Kinderh., 1911, Orig. iii, 28.

4. Vipond: Arch. Pediatrics, xxviii, 1911, p. 564; Canad. Med. Assn. Jour., November, 1911, p. 329.

5. Koessler and Koessler: Jour. Infect. Dis., Nov. 9, 1911.

6. Leede: München. med. Wchnschr., 1911, lviii, 293 and 1673.

In 200 cases of scarlet fever the sign was absent only once, and that was in an extremely fat girl. The sign can usually be elicited several weeks after the onset, and in one case, complicated by nephritis, was present after 104 days.

Strauch[7] employed this test in 340 cases, including sick and well of all ages. It was present in about half of 160 individuals in health (45 per cent.). Girls showed much less tendency to react than boys. Of 180 sick persons, 107 were positive (56 per cent.). The scarlet fever (twenty-three), and the measles cases (thirteen) all reacted. It was present in various percentages in many other diseases, and in 100 per cent. of blood diseases. Mayr[8] found the phenomenon in twenty out of 100 cases of skin and venereal diseases. Leede in a later communication states that he did not claim that the sign is pathognomonic, but that it is the most constant symptom in scarlet fever and therefore is of great negative value. Leede tested the sign in certain blood diseases without reaction, contrary to the findings of Strauch.

Pastia[9] describes a linear erythematous exanthem which is localized on the flexor surface of the elbow joint. The phenomenon appears at the same time as the rash appears and remains as a linear pigmentation after the rash has disappeared. He believes that the sign will bear the same relation to scarlet fever that Koplik spots do to measles.

THE DIAZO REACTION IN SCARLET FEVER

Woody and Kolmer,[10] guided by the results of the study of the diazo reaction in 502 cases of scarlet fever, conclude that its value is very slight in differentiating scarlet fever from serum disease, because of the comparatively low and inconstant percentage of positive reactions in both of these diseases. It was positive in 17.3 per cent. of scarlet fever and 12.9 per cent. of diphtheria cases in the first week. They found it in 10.8 per cent. of the cases of serum disease, some of which may have been due to diphtheria. These results are contrary to those of Ker, who previously found the reaction negative in serum disease.

MENINGEAL SYMPTOMS IN SCARLET FEVER

Sachs[11] reports a series of 400 cases of scarlet fever, sixteen of which showed meningeal symptoms without increased intraspinal pressure — the condition known as meningismus.

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7. Strauch: München. med. Wchnschr., 1911, lviii, 1761.
8. Mayr: München. med. Wchnschr., 1911, lviii, 1359.
9. Pastia: Arch. de méd. d. enf., February, 1911, p. 14.
10. Woody and Kolmer: Arch. Pediat., January, 1912.
11. Sachs: Jahrb. f. Kinderh., lxxxiii, (Supplement).

LUMBAR PUNCTURE IN UREMIA FOLLOWING SCARLET FEVER

Allaria[12] and Sheffield[13] each report a case of uremic coma following scarlatinal nephritis, both of which recovered almost immediately following lumbar puncture. Sheffield believes that a hypodermic of morphin (0.004) and atropin (0.0001) aided in the recovery of his patient.

THYROID IN SCARLET FEVER

Bauer[14] reports three cases of thyroiditis, without serious symptoms, occurring from eleven to forty-six days after the onset.

DIABETES FOLLOWING SCARLET FEVER

Brice[15] reports a case of rapidly fatal diabetes developing seven weeks after the onset of a mild scarlet fever.

PROPHYLAXIS IN SCARLET FEVER

Vaccine.—Roszkowski and Czarkowski[16] in seventy-nine cases employed vaccine, prepared from an attenuated culture of scarlatinal streptococci, as a prophylactic measure, with marked success. They divide their cases into three groups; all were vaccinated.

Group I, thirty-three children, not isolated. Three developed a mild scarlet fever, while among unvaccinated relatives, one death and two severe cases developed.

Group II, eleven patients, isolated. No cases developed.

Group III, thirty-five girls in an institution in which there were three severe cases at time of vaccination. No cases developed.

DIPHTHERIA ANTITOXIN AS A PROPHYLAXIS IN SCARLET FEVER

Benjamin and Witzinger[17] believe that the injection of diphtheria antitoxin has an attenuating effect on an ensuing scarlet fever. Their observations cover 138 cases of scarlet fever which had received diphtheria antitoxin before scarlet fever symptoms had developed. The fever lasted only one day in 76.2 per cent. of the cases, two days in 4.8 per cent. and over three days in 19 per cent. in those cases which had had antitoxin. In those cases which had received no injections the figures are 8.5 per cent., 16.4 per cent., and 75 per cent., respectively.

The investigators believe that the antitoxin is of prophylactic value and suggest the injection of serums of different origins to prolong the period of efficiency of the serums.

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12. Allaria: Gaz. d. osp., 1911, xxxii, p. 1291.
13. Sheffield: Zentralbl. f. Kinderh., 1911, xvi, 169.
14. Bauer: Monatschr. f. Kinderh., 1911, ix, p. 560.
15. Brice: Midland Med. Jour., 1911, x, 180.
16. Roszkowski and Czarkowski: Przeglad Pedyatryczny, 1911, iii, Abstr. in Ztschr. f. Kinderh., 1911, i, 7, 608.
17. Benjamin and Witzinger: Ztschr. f. Kinderh., 1911, Orig. ii, 123.

In a paper before the New York Academy of Medicine J. A. Kolmer[18] gave the results of his investigations on the glands in twenty-six cases of scarlet fever. He failed to find any organisms resembling those described by Vipond. Confident that scarlet fever streptococci did not possess any specific cultural or morphologic characteristics, he began to study the antibodies of a number of different cultures from various sources, with two main objects in view:

1. To gain, if possible, by such a study, a more accurate knowledge of the relation of streptococci to scarlet fever.

2. To determine if the prophylactic injections of streptococcus bacterins (vaccines) as practiced in Russia could be supported by laboratory investigation.

His investigations led to the following deductions:

1. A streptococcus produced a specific antibody up to a certain limit. The specific nature of these antibodies was seen by complement-fixation reactions in high dilutions between a streptococcus-immune serum and its antigen. With low dilutions the specific nature of the antibody was not brought out.

2. Not only did scarlet fever streptococci tend to produce their own specific immune serum, but likewise the streptococcus causing septicemia and that causing non-scarlatinal angina, etc., tended to produce their own immune serums. Therefore it did not seem any more justifiable to claim a specific streptococcus for scarlet fever than a specific streptococcus for septicemia and other conditions.

3. Finding but 11.2 per cent. positive reactions in scarlet fever tended to show that streptococcus infection in scarlet fever severe enough to produce immune bodies was not so common as generally believed.

One of the three toxic or malignant cases yielded a positive reaction. These severe cases were frequently due to an overwhelming effect of the true scarlet fever virus, without secondary streptococcus infection.

Since it has practically been proved that streptococci are not the cause of scarlet fever, it is difficult, according to Kolmer, to believe that immunization with streptococci can prevent the disease. Such immunizations might be valuable, he believes, in preventing the secondary streptococcic infections which occur in 11 per cent. of the cases of scarlet fever. His studies led to the following conclusions:

1. It is possible to raise the streptococci-opsonic index by the injection of organisms killed by an exposure to 60 C. for an hour.

2. The increase in the quantity of opsonin after three injections is so slight as to make the likelihood of establishing immunity against streptococcic infection dubious.

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18. J. A. Kolmer: Tr. New York Acad. Med., reported in Jour. Am. Med. Assn. Dec. 9, 1911, p. 1942, and in Arch. Pediat., December, 1911, p. 1005.

3. The opsonins are more or less specific toward the strains used in the process of immunization.

He further concluded that:

1. Streptococcus agglutinins are produced slowly by experimental immunization and the quantity is quite variable.

2. These agglutinins are apparently non-specific in character and of no value in differentiating streptococci.

3. They are demonstrable in 12.5 per cent. of scarlet fever patients but only in a comparatively low dilution of serum.

4. There is no relation between agglutinins and complement-fixation antibodies or between agglutinins and opsonins.

If a claim is made that there is a specific streptococcus for scarlet fever, a similar claim may be made for every other streptococcus, says Kolmer. The streptococcus found in scarlet fever belongs to the general class of streptococci, and is modified in some way during the course of the infection so as to give it a somewhat specific antibody and, occasionally, temporary cultural characteristics. This is also true of streptococci causing septicemia and simple sore throat. The reports of Russian physicians regarding the efficacy of injections of streptococcus vaccine, although apparently convincing, should be viewed with skepticism.

M. Nicoll, Jr., in discussing the paper read by Kolmer, stated that after a large experience in the use of antistreptococcus serum, he does not advise it except in cases resembling general septicemia. However, he has found that the local application of antistreptococcus serum to the mucous membrane of the pharynx and tonsils, frequently and freely applied, produced beneficial results.

DIPHTHERIA

HIGH DEATH-RATE OF DIPHTHERIA IN THE UNITED STATES

Hill[20] calls attention to the unnecessarily high death-rate from diphtheria in the United States. In practically every state in the union the percentage is high, averaging over twenty-five deaths per 100,000 as compared with only seven deaths per 100,000 in Paris. Hill believes that this is due to ineffective prophylactic measures, diagnoses made too late, and insufficient dosage of antitoxin in severe cases.

STAPHYLOCOCCUS SPRAY IN DIPHTHERIA CARRIERS

Page[21] reports a case which he treated according to the ideas laid down by Schiötz in 1909. Schiötz noticed that patients with staphylococcus sore throats did not contract diphtheria if placed in the diphtheria wards,

20. Hill: Med. Record, April 1, 1911, p. 568.

21. Page: Arch. Int. Med., January, 1911, p. 16; New York Med. Jour., December 23, 1911.

and that staphylococcus sore throats often terminated positive diphtheria bacterial findings. Six diphtheria carriers were treated by sprays of a pure culture of *Staphylococcus aureus* with marked success.

Page's case was a diphtheria convalescent whose throat contained virulent bacilli three months after clinical symptoms had vanished. The staphylococcus culture was used as a spray every two hours, and on the third day the bacilli could no longer be found.

Catlin, Scott and Day[22] employed this procedure in eight nurses who were carrying diphtheria in spite of all treatment. All of the cases yielded to this method of treatment in a short time.

Up to the present the results have been remarkably successful and no harmful results have been caused by the staphylococcus.

ACTIVE IMMUNITY AGAINST DIPHTHERIA

Blumenau,[23] Dsershovsky and Boldireff[24] and other Russian observers, by subcutaneous injections and local applications of diphtheria toxin to the nares, have produced active immunity to diphtheria in a number of cases. Small doses of the toxin were employed and the immunity was of longer standing than in cases which have received passive immunization with antitoxin.

ACETONURIA IN DIPHTHERIA

F. Reich[25] examined the urine in 3,200 cases of diphtheria and found acetone, by the sodium nitropruside test, present in 65 per cent. of the cases. Its frequency showed a direct relation to the severity of the attack, as it was present in 57.4 per cent. of the mild, 71.1 per cent. of the moderate and 80.3 per cent. of the severest cases. As it was found in 40.2 per cent. of non-diphtheritic throat inflammations its value as a diagnostic sign cannot be considered of great importance.

BLOOD-PRESSURE IN DIPHTHERIA

Rolleston[26] in a series of 179 cases of diphtheria found the blood-pressure subnormal in sixty-three patients, or 35.1 per cent., the extent and duration of the depression having, as a rule, a direct relation to the severity of the infection. High readings were obtained in the laryngeal and uremic cases. He concludes that sphygmomanometry in diphtheria, as in other acute disease, though of considerable theoretical interest, has little practical significance.

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22. Catlin, Scott and Day: Jour. Am. Med. Assn., Oct. 28, 1911, p. 1452.
23. Blumenau: Vratch, 1911, No. 5.
24. Dsershovsky and Boldireff: New York Med. Record, May 6, 1911, p. 819.
25. Reich: München. med. Wchnschr., 1911, lviii, 2153.
26. Rolleston: Brit. Jour. Child. Dis., 1911, viii, 433.

L. L. Smith[27] reports a case of vulvovaginitis resembling gonorrhea in a 3-year-old girl. Smears from the mucopurulent discharge showed a pure culture of diphtheria bacilli. The throat was clear. Seven thousand units of antitoxin were given in the course of a few days and the inflammation subsided. The source of infection in this case was probably a bath towel used by a visitor who had been exposed to diphtheria and was suffering from a "cold" during her stay.

NASAL DIPHTHERIA

De Biehler and Dazskiewicz[28] report seven cases of apparently simple coryza, with few constitutional symptoms, which were really due to diphtheria, and were cured by antitoxin. They believe that the condition is more common than is supposed and urge the employment of cultures in cases in which operation is being considered and in persistent coryza.

GANGRENE FOLLOWING DIPHTHERIA

Ransome and Corner[29] and H. Kramer[30] report cases of gangrene of the leg in the second week of diphtheria.

ORGANOTHERAPY IN SERUM DISEASE

R. Wallace[31] suggests that the sudden death which may occur after the injection of serum into sensitized persons or those subject to bronchial asthma, is due to insufficiency of the suprarenal glands. He recommends the hypodermic injection of suprarenalin (adrenalin) both as a prophylactic and curative measure.

Hodgson[32] attempted to attenuate or prevent manifestation of serum sickness after injection of antitoxin by the administration of thyroid extract in small doses for four to six days. In about fifty cases this procedure appeared to have a good effect as compared with fifty cases in which the gland substance was not used.

VINCENT'S ANGINA ORGANISMS IN OTHER DISEASES

Blühdorn[33] examined smears from the throats of 222 patients, including cases of sore throat in various diseases, and healthy mouths, for the spirilla and fusiform bacilli present in Vincent's angina. He found both organisms, or one of them in

49 out of 76 cases of diphtheria.
11 out of 42 cases of .scarlet fever.

27. Smith, L. L.: New York Med. Jour., 1911, i, 24.
28. DeBiehler and Dazskiewicz, Arch. de méd. d. enf., November, 1911.
29. Ransome and Corner: Lancet, London, 1911, i, 94.
30. Kramer: Brit. Med. Jour., 1911, ii, p. 505.
31. Wallace: Med. Rec., New York, Jan. 7, 1911, p. 15.
32. Hodgson: Lancet, London, 1911, clxxx, 373.
33. Blühdorn: Deutsch. med. Wchnschr., June 22, 1911, xxxvii.

13 out of 26 cases of sore throat due to staphylococci and streptococci.
2 out of 4 cases of ulcerative stomatitis.
21 out of 31 cases of syphilis of mouth and throat.
22 out of 40 cases of healthy mouths.

These results make it evident that the clinical picture and smear may be inconclusive. Diphtheria must be excluded by a culture in every case.

DIPHTHERIA ANTITOXIN BY MOUTH

Cumberledge[34] has obtained good results with the oral administration of antitoxin. Results were obtained within a few hours, the patients showed no signs of serum sickness and were also spared the pain and discomfort of a hypodermic injection. An average of 2,000 units was given, and in some cases as a mixture in small dosage every two to four hours.

CHICKEN-POX

Magnan and de la Riboissière[35] report that they have found a fine Gram-negative bacillus in the vesicle of chicken-pox. The culture of the bacillus has been without result so far.

EPIDEMIC OF VARICELLA

Bondy[36] had the opportunity of observing an epidemic of chicken-pox in an orphanage at Warsaw. Of eighty-three infants, most of them under 6 months of age, twenty-seven were infected with the disease. A diffuse erythematous rash was observed one or two days before the varicella lesions appeared in eight cases, five of which resembled scarlet fever and three measles. No eruption was found on the mucous membrane of the mouth or throat. In some atrophic children, abscesses developed on the site of the lesion, which in two cases led to death from general sepsis. In three out of four cases complicated by measles the patients died of bronchopneumonia.

Luth[37] reports a case of herpes zoster in a woman whose baby was shortly after taken sick with chicken-pox. This close association of the two diseases has often been observed and the author does not believe that the connection is purely accidental.

WHOOPING COUGH

Wernstedt,[38] in a recent epidemic of pertussis, found a close and constant connection between the spasmophilic diathesis and the severe

34. Cumberledge: Brit. Med. Jour., July 8, 1911.
35. Magnan and de la Riboissière: Compt. rend. Soc. de biol., 1911, lxx, 309.
36. Bondy: Przeglad Pedyatryczny, 1911, iii, 177; Abstr. Ztschr. f. Kinderh., i, 7, p. 608, 1911.
37. Luth: Monatsh. f. prakt. Dermat., 1911, lii, 622.
38. Wernstedt: Hygeia, Stockholm, lxiii, No. 7, Abstr. Jour. Am. Med. Ann., 1911, p. 1652.

spasmodic coughing in pertussis. The severe forms of the latter, he believes, are indications of a neuropathic constitution.

Mehnert[39] believes that ordinary small-pox vaccination has an attenuating effect on the spasmodic cough in pertussis. He vaccinated his patients as soon as a diagnosis of whooping-cough was made, and as soon as the pustule appeared the paroxysms became milder and disappeared within fifteen days at a maximum.

TYPHOID FEVER

BASS-WATKINS TYPHOID AGGLUTINATION TEST IN CHILDREN

Menville[40] employed the Bass-Watkins typhoid agglutination test on some eighty children and obtained positive results in all cases that proved to be typhoid. He follows the procedure as recommended by the originators — one-quarter of a drop of blood is smeared on the middle of a glass slide in the usual manner. The blood is then ready to be examined at any time. To make the test one drop of water is dropped over the blood and the blood dissolves within a quarter of a minute. With the same dropper one drop of typhoid suspension is placed on the center of the diluted blood. The slide is gently agitated until the reaction has shown itself positive; or for two minutes before it is called negative. A strong positive reaction appears often within a half minute. In the presence of positive blood, the agglutination in the blood serum causes the typhoid bacilli to stick together and to collect into a fine or coarse grayish, granular sediment, visible to the naked eye. Rapidly formed coarse granules indicate a strong reaction and fine granules a weak one. Fluid that is uniformly cloudy and shows no granules denotes a negative reaction. The test is recommended because of its apparent reliability and the simplicity with which it can be carried out.

TYPHOID IN INFANTS

Achard and Flandrin[41] report a case of typhoid in an infant, the third in their experience. The child was 11 months old, breast-fed and ran a course of thirteen days with symptoms of fever and depression and gastro-intestinal disturbances. No typhoid was discerned in the neighborhood. They believe that typhoid would be considered a less rare condition if serodiagnostic measures were applied to infants more regularly.

Kaspar[42] describes a case in an infant 10 weeks old, beginning with suppuration in the knee joint. The pus aspirated showed pure cultures of typhoid bacilli, as did the urine.

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39. Mehnert: Jahrb. f. Kinderh., June, 1911, lxxiii, No. 6.
40. Menville: Arch. Pediat., March, 1912.
41. Achard and Flandrin: de Progrès méd., 1911, p. 277.
42. Kaspar: Monatsch. f. Kinderh., 9, 1911, p. 953.

MEASLES

EXPERIMENTAL WORK

During the past year Goldberger and Anderson[43] have reported some interesting observations on the transmission of measles to monkeys.

In 1898 Chavigny reported a case of measles in a monkey which had been exposed to a keeper suffering from measles. Josias in attempting to produce the disease in monkeys by exposure to children with measles failed in all his experiments. Grünbaum in 1904 attempted to produce the disease in two chimpanzees without success, and concluded that he had probably conferred immunity, rather than transmitted infection. It is believed that monkeys alone, of the lower animals, are susceptible to measles, but further investigation may prove this to be an error, as the experiments of Goldberger and Anderson were often negative in their monkeys.

In the experiments of Anderson and Goldberger blood was taken from undoubted cases of measles, defibrinated, and injected in amounts varying from 2.5 c.c. to 5 c.c. into the peritoneal cavity, under the dura, and into the heart. Nine animals were injected with blood from four undoubted cases of measles. Four of the monkeys showed positive reactions, with variable results.

The rash in a typical case appeared about ten days after the inoculation, first on the scalp, extending downward over the abdomen, back and limbs within the next two days. On the third day the rash began to fade and on the sixth day was scarcely perceptible. The temperature curve was similar to that in the child, reaching its height with the appearance of the eruption and falling as the rash disappeared. As in children, the temperature curve varied in the different monkeys. Some of the animals showed involvement of the respiratory mucous membrane, as evidenced by sneezing and coughing. No observations regarding Koplik's spots are recorded.

From the experiments of Goldberger and Anderson it appears that the blood is especially infective just before and during the first twenty-four hours of the eruption, after which it becomes progressively less infective.

The virus is filterable and can be passed through a Berkefeld filter.

Experiments with the mouth and nose secretions show that these secretions are infective at the time the rash appears. In three experiments with the scales the results were negative.

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43. Goldberger and Anderson: Pub. Health Rep., June 9, 1911, p. 847; ibid, June 16, 1911, p. 887; Jour. Am. Med. Assn., July 8, 1911, p. 113; Aug. 5, 1911, p. 476; Sept. 16, 1911, p. 971; Nov. 11, 1911, p. 1612.

Hektoen[44] later obtained results similar to those of Goldberger and Anderson and made observations regarding the blood-findings in the measles of monkeys. He found practically the same changes as in human measles. There is a preliminary leukocytosis followed by a leukopenia, chiefly of the polymorphonuclear neutrophils, the lymphocytes being relatively increased.

104 South Michigan Boulevard.

44. Hektoen: Jour. Am. Med. Assn., Dec. 2, 1911.

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